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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup>:
C12N 15/12, C07K 14/705, 16/28, C12N 5/10, G01N 33/68

(11) International Publication Number:

WO 99/29847

(43) International Publication Date:

17 June 1999 (17.06.99)

(21) International Application Number:

PCT/US98/23161

**A1** 

(22) International Filing Date:

30 October 1998 (30.10.98)

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

(30) Priority Data:

08/985,809

5 December 1997 (05.12.97)

us

**Published** 

With international search report.

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(54) Title: T-TYPE VOLTAGE-GATED CALCIUM CHANNELS AND METHOD OF USING SAME

(57) Abstract

The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel and cells and cell lines expressing such nucleic acids. The present invention also provides an isolated or substantially purified T-type calcium channel and an isolated or substantially purified antibody molecule recognizing an epitope on a T-type calcium channel protein.

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# T-TYPE VOLTAGE-GATED CALCIUM CHANNELS AND METHOD OF USING SAME

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#### TECHNICAL FIELD OF THE INVENTION

The present invention relates to cloned T-type calcium channels.

#### **BACKGROUND OF THE INVENTION**

Biological membranes are themselves generally impermeable to ionic species. Thus, ions enter cells through regulated pores formed from membrane-associated proteins. Most of these regulated pores are voltage-dependent and are thus able to transduce changes in the transmembrane potential into ion flux. Voltage-gated ion channels form a "superfamily" of related proteins (cf. Jan et al., *Nature*, 345, 672 (1990)). Peculiar to this genus is a high degree of conservation in molecular structure. Generally, voltage-gated channels are membrane bound glycolsylated proteins formed of many subunits. Large α subunits form a pore in the membrane that is selective for a given ionic species. Each α subunit contains four domains (I, II, III, and IV). Each channel domain has six putative transmembrane helical segments (S<sub>1</sub>-S<sub>6</sub>). In general, the segments within each domain are similar but not identical. Aside from overall structural conservation, certain charged residues within the domains are highly conserved among voltage-gated ion channels (Jan et al., *supra*; Stühmer et al., *Nature*, 339, 597-603 (1989)).

Differences in charged residues between groups of voltage-gated ion channels confer properties unique to each subgroup, such as ion selectivity. For example, most voltage gated ion channels are selective for either sodium, potassium or calcium. Known calcium channels require a ring of negative charge provided by glutamate residues found at similar locations in each of the domains (Yang et al., *Nature*, 366, 158-61 (1993)).

Voltage-gated channels are often classified on the basis of their electrophysiology. The resting membrane potential of most animal cells is between about -70 mV and -80 mV. When the membrane becomes depolarized (moved towards 0 mV), various membrane channels become activated (they are said to

"open"). Thus, one basis for classifying membrane channels is the membrane potential necessary to activate (or "gate") them (voltage dependency). For example, "T-type" calcium channels are activated at a lower voltage than L- or N-type channels (Nowycky et al., *Nature*, 316, 440-43 (1985)). Other physiological properties are the activation kinetics, inactivation kinetics, tail current (deactivation kinetics), and single channel conductance. Thus, in comparison to other calcium currents. T-type calcium current is characteristically short (Chen et al., *J. Gen. Physiol.*, 96, 603-30 (1990)), and it exhibits characteristically slow activation kinetics near threshold. fast inactivation kinetics, and slow tail current (Randall et al., *Neuropharmacol.*, 63, 879-93 (1997); Carbone et al., *Nature*, 310, 501-02 (1984); Nilius et al., *Nature*, 316, 443-46 (1985)).

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Calcium currents have been implicated in many neurological and muscular functions. For example, T-type calcium current is associated with cardiac pacemaker activity, pain transmission in the central nervous system, and in other physiological functions. Defects in T-type calcium current have been implicated in cardiac arrhythmia, hypertension, and epilepsy. Given their potential clinical value, the pharmacological properties of calcium channels have been the subject of extensive study. Most such studies have involved L-type channels because, unlike T-type channels, L-type calcium channels are readily purified from cell extracts. For example, L-type calcium channels have been purified using dihydropyridine drugs (e.g., nifedipine) which can bind with sufficiently high affinity to serve as a ligand for purifying L-type calcium channels. Such purified and cloned L-type calcium channels have been used to develop assays for drugs affecting L-type calcium channels (see, e.g., U.S. Patents 5,429,921 and 5,386,025).

While many electrophysiological characteristics of T-type calcium currents are known, the lack of isolated T-type channels has stalled research into the pharmacology and biophysics underlying the T-type calcium current, at least in comparison with other calcium channels. Indeed, while it is generally assumed that voltage-sensitive ion channels are responsible for the current, no such channel protein, nor any nucleic acid encoding such a protein, has been isolated. In view of the foregoing problems, there exists a need for an isolated T-type calcium channel and a nucleic acid encoding a T-type calcium channel.

#### **BRIEF SUMMARY OF THE INVENTION**

The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel and cells and cell lines expressing such nucleic acids. The present invention also provides an isolated or substantially purified T-type calcium channel and an isolated or

substantially purified antibody molecule recognizing an epitope on a T-type calcium channel protein.

The present invention is useful for exploring the electrophysiology and pharmacology of the T-type calcium current. Such knowledge can lead to the development of drugs for potentiating or attenuating T-type calcium channels. Thus, the present invention provides an assay for identifying potential drugs affecting T-type calcium channels by exposing cells expressing a T-type calcium channel to a putative drug and then measuring the calcium flux in response to a change in membrane potential. The identification of drugs affecting T-type calcium channels will facilitate even greater understanding of the biophysics of these proteins. Furthermore, some such drugs could have potential clinical applications.

The invention can best be understood with reference to the accompanying drawings and in the following detailed description of the preferred embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1E compare the complete amino acid sequences of three types of T-type calcium channels ( $\alpha$ 1G (or Ca,T.1),  $\alpha$ 1H (or Ca,T.2), and  $\alpha$ 1I (or Ca,T.3)), indicating conserved functional domains.

Figures 2A-2D are graphic representations of the current-voltage relationships of three cloned T-type calcium channels (Figures 2A, 2B, and 2C) and a cloned R-type calcium channel (Figure 2D).

Figure 3A is a graphic representation of the average current-voltage curve for cloned T-type calcium channels ( $\alpha$ 1G, triangles,  $\alpha$ 1H, inverted triangles,  $\alpha$ 1I, circles), and a cloned R-type calcium channel (filled squares). Figure 3B compares the normalized conductance of a cloned T-type calcium channel at three different concentrations of BaCl<sub>2</sub>.

Figure 4 depicts average kinetics of the tail current as a function of repolarization potential for  $\alpha 1G$  (triangles),  $\alpha 1H$  (inverted triangles),  $\alpha 1I$  (circles), and a cloned R-type calcium channel (filled squares).

Figures 5A and 5B graphically present data concerning the use of a cloned T-type calcium channel to detect drugs affecting the channel. Figure 6A depicts the effect of  $100~\mu M$  on current-voltage relationships with a single dosage of miberfradil. Figure 6B illustrates the effect on T-type channel conductance of various doses of miberfradil.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel  $\alpha$ 

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subunit. The nucleic acid can be of any type, and it can include other elements aside from a sequence encoding a T-type calcium channel domain or domains. For example, where the nucleic acid comprises RNA, it can also include regulatory sequences suitable to permit translation of the RNA. Thus, an RNA nucleic acid of the present invention preferably has at least one ribosome entry site, and preferably has a polyadenosine tail for stabilizing the RNA in the cellular environment. Similarly, DNA nucleic acids of the present invention can have regulatory elements for promoting the transcription of sequence encoding the T-type calcium channel into an RNA such as that described above. For example, a DNA nucleic acid of the present invention can have a promoter and/or an enhancer sequence. While the nucleic acid can be any type of nucleic acid, the nucleic acid preferably comprises a cDNA. A cDNA nucleic acid is preferred over other nucleic acids to permit the nucleic acid to be readily cloned, sequenced, and expressed in a wide variety of cells.

The choice of promoter and/or an enhancer will largely depend on the milieu in which the nucleic acid is to be expressed. Thus, for expression in bacterial cells, the regulatory elements are bacterial promoters. Similarly, for expression in mammalian cells, the regulatory elements are able to effect expression in mammalian cells. While many such regulatory elements are known in the art, examples include prokaryotic promoters and viral promoters (e.g., retroviral ITRs, LTRs, immediate early viral promoters (IEp), such as herpesvirus IEp (e.g., ICP4-IEp and ICP0-IEp), cytomegalovirus (CMV) IEp, and other viral promoters, such as Rous Sarcoma Virus (RSV) promoters, and Murine Leukemia Virus (MLV) promoters). Other suitable promoters are eukaryotic promoters, such as enhancers (e.g., the rabbit β-globin regulatory elements), constitutively active promoters (e.g., the β-actin promoter, etc.), signal specific promoters (e.g., inducible promoters such as a promoter responsive to RU486, etc.), and tissue-specific promoters (e.g., those active in epidermal tissue, dermal tissue, tissue of the digestive organs (e.g., cells of the esophagus, stomach, intestines, colon, etc., or their related glands), smooth muscles, such as vascular smooth muscles, cardiac muscles, skeletal muscles, lung tissue, hepatocytes, lymphocytes, endothelial cells, sclerocytes, kidney cells, glandular cells (e.g., those in the thymus, ovaries, testicles, pancreas, adrenals, pituitary, etc.), tumor cells, cells in connective tissue, cells in the central nervous system (e.g., neurons, neuralgia, etc.), cells in the peripheral nervous system, and other cells of interest).

The isolated or substantially purified nucleic acid of the present invention encodes all or part of a T-type calcium channel  $\alpha$  subunit. As used herein, a "calcium channel" includes a protein structure for facilitating the flux of calcium ions across a biological membrane into which the calcium channel is inserted. As used herein, a "T-type channel" is a type of voltage-gated ion channel that facilitates the flux of ions

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when the membrane potential of a biological membrane into which it is inserted experiences a slight depolarization. Thus, a T-type calcium channel can begin to gate from about -60 mV to about -30 mV (i.e., about -45 mV to about -35 mV) in about 10 mM Ba<sup>2+</sup>. Additionally, T-type channels of the present invention exhibit a slow deactivation (tail current) following depolarization. Thus, a T-type calcium channel can exhibit a tail current that decays exponentially with a tau value from about 1 ms to about 10 ms (e.g., from about 4 ms to about 7 ms, such as about 6 ms) following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a Ba<sup>2+</sup> concentration of from about 10 mM to about 40 mM. Another defining characteristic of T-type calcium channels is that they exhibit small single channel conductance. Thus, for example, a T-type channel exhibits a single channel conductance of from about 4 pS to about 12 pS (e.g., from about 6 pS to about 10 pS), and typically from about 7 pS to about 9 pS in a solution with a Ba<sup>2+</sup> concentration of about 0.1 M.

The isolated or substantially purified nucleic acid of the present invention encodes all or part of any T-type calcium channel having at least one of the aforementioned electrophysiological properties when properly assembled within a cellular membrane. The general structure of calcium channels is summarized above and is otherwise known in the art. Thus, for example, the nucleic acid can encode one of the four functional domains mentioned above. As used herein, a domain of a Ttype calcium channel is any protein structure able to associate with three other domains to form a tetrameric body functioning as a T-type calcium channel. While the native T-type calcium channel structure includes all four domains in a single polypeptide (indicated in Figures 1A-1E), a domain can exist as a polypeptide species separate from those containing the other domains. Such separate domains are able to associate within the plasma membrane to form a functional channel. Alternatively, where a plurality of domains are linked within a common polypeptide, the linkage can deviate substantially from the native linkage. Thus, for example, the domains can be linked by polypeptide sequences other than those sequences linking the domains in the native protein (e.g., non-native polyglutamate linkages). Indeed, the domains themselves can include non-native linkages between membrane-spanning elements within the domains. Aside from these modifications, the nucleic acid can encode a chimeric calcium channel domain (or an entire channel) comprising a portion of a Ttype calcium channel and a portion derived from another calcium channel (or other channel) protein. For example, the chimera can include portions of domains from Ttype channels responsible for low voltage gating and portions of domains from other calcium channels responsible for slow inactivation. Such a protein exhibiting T-type gating but longer inactivation kinetics would facilitate pharmacological research.

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As mentioned, nucleic acids of the present invention can encode an entire Ttype channel (i.e., a T-type channel protein comprising four functional domains). It has been discovered that at least three genes encoding T-type calcium channels exist in humans and rats (i.e.,  $\alpha 1G$  (or Ca,T.1),  $\alpha 1H$  (or Ca,T.2), and  $\alpha 1I$  (or Ca,T.3)), and alternate splicing of these isoforms exist. Examples of the amino acid sequences of full-length T-type channels, and the sequences of suitable coding nucleic acids are set forth at SEQ ID NOs:1-8 (α1G sequences). SEQ IS NOs:9-10 (α1H sequences), and SEQ ID NOs: 11-12 (all sequences). However, the invention is not limited to these exemplary sequences. Indeed, as mentioned, an amino acid sequence of a T-type calcium channel can vary from those listed, and it is within the state of the art to change a nucleotide sequence encoding a T-type channel to introduce mutations into the protein. Indeed, for conducting electrophysiological assays, it may be desirable to introduce mutations into such a protein. For example, mutations comprising insertions or deletions can be introduced on either the amino- or carboxy-terminus of the protein, or such mutations can be intrasequence insertions or deletions. Where the electrophysiological properties of the calcium channel are to be conserved, such mutations preferably are in regions other than the membrane spanning domains. However, in some applications (e.g., to decrease inactivation kinetics), the changes can be within the membrane-spanning regions. Moreover, as mentioned above, the sequence can form a protein having only one functional domain of a T-type calcium channel. Additionally, the sequence can also form a chimeric protein or domain, such as those described above.

Aside from insertions and deletion mutations of native T-type calcium channel sequences. a T-type calcium channel can include substitutions of amino acid residues. e.g., for those indicated in SEQ ID NOs:1-12. Preferably, and especially where such a substitution is within a membrane spanning region, the substitution is conservative. Thus, within membrane spanning domains, positively-charged residues (H, K, and R) preferably are only substituted with positively-charged residues; negatively-charged residues (D and E) preferably are only substituted with negatively-charged residues; neutral polar residues (C, G, N, Q, S, T, and Y) preferably are only substituted with neutral polar residues; and neutral non-polar residues (A, F, I, L, M, P, V, and W) preferably are only substituted with neutral non-polar residues. Preferably, any amino-acid substitution within the membrane-spanning regions does not alter this conservation. Most preferably, any substitution, deletion, or insertion does not alter the IVS4 domain. In each of the exemplary T-type calcium channel  $\alpha$  subunit sequences, the putative IVS4 region comprises SEQ ID NO:13. Given the strong sequence conservation among families of voltage-gated ion channels, it is likely that this sequence or a derivative sequence, will be present in T-type channels. Thus, the

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present invention provides any T-type calcium channel (or a nucleic acid encoding such a T-type calcium channel) comprising SEQ ID NO:13 or a sequence derived from SEQ ID NO:13 having conservative amino acid substitutions. as described above.

The nucleic acid of the present invention encoding all or a part of a T-type calcium channel can be isolated via any suitable method. For example, prior to the present invention, one of skill in the art could design a probe based on the sequence of known, non-T-type, calcium channels and use such probe to screen a genetic library. If such a screen were to identify a putative calcium channel, the researcher could then attempt to clone the entire nucleic acid to characterize it. Similarly, prior to the present invention, to isolate a nucleic acid encoding a T-type calcium channel, one of skill in the art could consult publicly available databases containing DNA sequences (e.g., Genbank) to locate nucleic or amino acid sequences representing a portion of a T-type calcium channel protein or nucleic acid. However, such databases contain no sequence for a full-length T-type calcium channel or identify any sequence as a T-type channel. Such methods assume that T-type calcium channels share sufficient sequence identity with known calcium channel nucleic acids to cross-hybridize, an assumption not supported by any published report. Moreover, prior to the present invention, no partial sequence in such databases was identified as corresponding to a T-type calcium channel. Thus, prior to the present invention, the presence of partial sequences in the public DNA databases could facilitate the isolation of T-type calcium channels only with the exercise of a considerable degree of speculation on the part of the researcher.

By providing several sequences pertaining to T-type calcium channels and a comparison presenting conserved regions and domains, the present invention greatly facilitates the isolation of other nucleic acids encoding T-type calcium channels (or derivatives thereof) with much less experimentation. Thus, while any of the methods discussed above can be employed to isolate other members of this genus, preferably, a nucleic acid encoding a T-type calcium channel is isolated by probing a genetic library using a probe that hybridizes to a DNA encoding a peptide sequence contained in (or similar to) a known T-type calcium channel (e.g., SEQ ID NOs:1-12). To facilitate the isolation of a T-type calcium channel, the present invention provides an isolated polynucleotide hybridizing to a portion of the nucleic acid of the present invention encoding a T-type calcium channel (or a portion thereof). Thus, for example, the present invention includes an isolated polynucleotide hybridizing to SEQ ID NO:1-12. The isolated polynucleotide can hybridize to all or any portion of the sequence encoding the T-type calcium channel.

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To isolate such a polynucleotide, any portion of a sequence encoding a T-type calcium channel can be employed as a probe to screen a genetic library, and such screening can be accomplished by standard techniques known in the art. While the probe can hybridize to any portion of such a DNA, preferably the probe is designed to hybridize to a DNA encoding a polypeptide sequence that is highly conserved among T-type calcium channels but is less conserved between the genus of T-type calcium channels and other proteins. Such peptide sequences are readily apparent from the sequence comparison set forth in Figures 1A-1E. Generally, the specificity of hybridization in a genetic screen varies depending on the length of the probe and the stringency (e.g., temperature, salt and detergent concentration, etc.) of hybridization. Stringency of hybridization is broadly classified as "high," "moderate," or "low," and the parameters of these terms are well recognized in the art (see, e.g., Sambrook et al., "Molecular Cloning, a Laboratory Manual," Cold Spring Harbor Press, 1989). The isolated polynucleotide hybridizing to a portion of the nucleic acid encoding a T-type calcium channel can hybridize under any desired stringency conditions. However, for identifying other T-type channels, preferably, the hybridization occurs under moderate stringency, and most preferably under high stringency.

Of course, the isolated or substantially purified polynucleotide can itself be employed as a probe to screen a library as described to isolate a second nucleic acid. In such a screen, one of the polynucleotides will be complementary to a portion of the sequence encoding the T-type calcium channel, and the other isolated nucleic acid will be "sense." Preferably, one of the two isolated polynucleotides (the "sense" strand) itself encodes a T-type calcium channel, or at least one domain thereof. Such a sequence can be cloned to be operably linked to suitable regulatory elements, as described, to produce a T-type calcium channel. Thus, aside from using the nucleic acid of the present invention to produce a T-type calcium channel, the nucleic acids of the present invention are also useful for isolating other sequences encoding T-type calcium channels, or derivatives thereof.

However isolated, the isolated or substantially purified nucleic acid of the present invention is useful, in part, for producing all or a portion of a T-type calcium channel. Thus, the nucleic acid can be introduced into a suitable milieu for driving its expression. Because T-type channels are transmembrane proteins, preferably such a milieu is a living cell. However, it should be understood that the nucleic acid can also be expressed *in vitro* under conditions, such as those known in the art, suitable for *in vitro* transcription and translation. However produced, the present invention includes any protein, such as a recombinant protein or an isolated or substantially purified protein, including all or a portion of a T-type calcium channel or a protein derived from a T-type calcium channel.

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For expression in a living cell, the nucleic acid must be introduced into the cell. As nucleic acids are generally introduced into cells as part of genetic vectors, the present invention provides a vector having a T-type calcium channel nucleic acid of the type described above. Any type of vector suitable for introducing the nucleic acid into a host cell is within the context of the present invention. Examples of such vectors include naked DNA and RNA vectors (such as oligonucleotides, plasmids, capped cRNA, etc.), viral vectors such as adeno-associated viral vectors (Berns et al., *Annals of the New York Academy of Sciences*, 772, 95-104 (1995)), adenoviral vectors (Bain et al., *Gene Therapy*, 1, S68 (1994)), herpesvirus vectors (Fink et al., *Ann. Rev. Neurosci.*, 19, 265-87 (1996)), packaged amplicons (Federoff et al., *Proc. Nat. Acad. Sci. USA*, 89, 1636-40 (1992)), pappiloma virus vectors, picornavirus vectors, polyoma virus vectors, retroviral vectors, SV40 viral vectors. vaccinia virus vectors, and other vectors. Once a given type of vector is selected, its genome must be manipulated for use as a background vector, after which it must be engineered to incorporate exogenous polynucleotides. Such manipulations are known in the art.

The vectors of the present invention are useful for introducing a nucleic acid encoding all or a portion of a T-type calcium channel into a host cell. Thus, the present invention provides a cell into which the vector of the present invention has been introduced. The host cell can be any cell suitable for expressing the nucleic acid (e.g., bacteria, insect cells, mammalian cells, etc.). The host cell can thus be *in vitro* or *in vivo*. Preferably the cells do not exhibit native T-type calcium current. A preferred cell type is HEK-293 cells because they contain genetic elements that facilitate the expression of transgenes from a variety of expression vectors. For facilitating electrophysiological recordings, oocytes (e.g., *Xenopus* oocytes) are preferred, as they are large and readily handled.

The vector can be introduced into the cell in any manner suitable for the cell type and vector employed. In one embodiment, the vector can be used to prepare an RNA transcript *in vitro* (e.g., a capped cRNA) which is then introduced into the host cell by standard methods (such as injection). Such techniques are preferred when the host cells do not actively transcribe DNA (such as oocytes). In other embodiments, a DNA vector is introduced into the cell such that it is transcribed within the cell. For example, the vector can be introduced into the cell such that it forms an extrachromosomal segment of genetic material in the cell, as is the case with many types of viral vectors. Alternatively, the vector can introduce the nucleic acid into the chromosomal DNA of the host cell.

Preferably, a cell into which the nucleic acid is introduced is also able to express the nucleic acid to produce the  $\alpha$  subunit protein. The expression of the nucleic acid can be detected by probing the cell for the presence of T-type calcium

channel mRNA, such as via Northern hybridization analysis, in situ hybridization, etc. More preferably, however, the cell is able to express the nucleic acid to produce the protein including all or a portion of a T-type calcium channel. In such cells, expression of the nucleic acid is confirmed by detecting the protein, for example, by probing cellular extracts with an antibody recognizing the protein (e.g., on a Western blot, etc.).

In the membrane of the cell producing the protein, the expressed protein contributes to the formation of a functional calcium channel. Where the protein encodes an entire  $\alpha$  subunit, the full protein will possess some or all of the electrophysiological properties of T-type calcium channels described above. Where the protein encodes less than an entire channel  $\alpha$  subunit (e.g., a domain), the protein will aggregate with other constituent domains in the membrane to form a functional channel. Thus, the presence of the protein can be detected by assaying the cell for T-type calcium channel activity. Indeed, assaying for channel activity serves to determine whether a nucleic acid encoding a putative calcium channel. in fact. encodes a species of T-type channel (as opposed to a member of another genus of calcium channels). For example, when large cells (e.g., oocytes) are used as the host cells, the electrophysiological properties of the channel can be investigated. Thus, the membrane activity of whole cells expressing the nucleic acid can be measured directly, such as via patch clamp techniques using a voltage clamp electrode and a current electrode (Bernal et al., J. Pharmacol. Exp. Ther., 282, 172-80 (1997)). Alternatively, the activity of single channels can be measured, such as with a standard depolarizing bath and pipette solutions (Lacerda et al., Biophys. J., 66, 183-43 (1994)). However measured, the properties of cells into which the putative nucleic acid is introduced are compared to the channel conductance, voltage dependency, activation kinetics, inactivation kinetics, or tail current known for T-type channels and discussed above. A measure of current density (e.g., pA/pF) can also be used to assess the level of gene expression in the cells, normalizing for cellular volume.

While, in accordance with the present invention, an isolated cell into which the T-type calcium channel nucleic acid has been introduced (and preferably stably expressing the nucleic acid to produce the protein) can be prepared, preferably, such transfection protocols result in a population consisting essentially of such transfected cells. For standardizing the results of many experiments, it is even more desirable to employ an established cell line consisting essentially of such cells. Preferably, for use in high throughput assays, cell lines stably expressing a T-type calcium channel exhibit a current density of at least about 40 pA/pF (e.g., at least about 45 pA/pF), such as about 50 pA/pF or even 55 pA/pF or higher. Preferably, a cell line in accordance with the present invention is able to propagate the nucleic acid through

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several passages (e.g., for at least 10 passages), and, preferably, the nucleic acid is stably integrated into the chromosomes of such cells. Thus, the cell line can propagate the nucleic acid for at least 20 passages, and more preferably significantly more than 20 passages (e.g., at least about 25 passages, or even more).

Regardless of the cell system, the ability to express a T-type calcium channel nucleic acid within host cells to produce an active channel permits the channel to be further studied. In this regard, the present invention provides a method of identifying. a drug which affects T-type calcium channels. The method involves first expressing a T-type calcium channel in a cell to produce an active channel, as herein described. The cell expressing the channel is then exposed to a solution containing a putative drug for interfering with the channel. Thereafter, the presence or absence of calcium flux in response to a change in membrane potential is assayed. Any such assay can be employed within the context of the present invention, (e.g., using labile dyes, radioisotopes (e.g., <sup>45</sup>Ca), recording electrophysiological changes in the membrane, etc.). A quick method of assaying for calcium flux is first to introduce a calcium-sensitive labile dye into the cells. For example, the dye can be one such as those that fluoresce or change color in the presence of calcium, many of which are known to those of skill in the art (e.g., Indo-1). Thereafter, the cells are exposed to a depolarizing solution containing high (e.g., about 50 mM) potassium concentration and a drug, and the reaction of the labile dye is compared to control cells. Using a labile dye affords the ability to assay many putative drugs quickly in a high throughput assay for putative drugs affecting T-type channels. For example, the initial screening can be carried out in 96 well plates. Moreover, dose-response data can be readily generated by exposing the cells to several concentrations of the same putative drug.

Once a putative drug is detected, its effect on the electrophysiology of the cell (e.g., single channel conductance, voltage dependency, activation kinetics, inactivation kinetics, and tail current of the cells) can be investigated in detail. Generally, the effect of the putative drug on T-type calcium currents is assessed by measuring the various electrophysiological parameters in the presence of various concentrations of the drugs and comparing the data to untreated (or sham-treated) control cells. Cells preferably are maintained in a continuous perfusion chamber during such experiments to facilitate changing solutions. The inventive method of identifying a drug which affects T-type calcium channels can employ any nucleic acid encoding a T-type calcium channel (or derivative thereof), such as those nucleic acids described herein. In fact, as several isoforms of T-type channel exist, the assay method can be repeated using nucleic acids encoding different isoforms to identify

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drugs that preferentially target a given isoform, or drugs which affect more than one isoform of T-type calcium channels.

Aside from affording an in vitro assay for detecting potential therapeutic or investigative drugs targeting T-type calcium channels, the method of expressing the T-type calcium channel nucleic acid can also be used in vivo. For example, as mentioned, several neurological and muscular diseases or disorders have implicated mutations affecting native nucleic acids encoding T-type calcium channels. The present invention, thus, provides a method of treating a disease or disorder associated with a deficiency in a native T-type calcium channel nucleic acid. The method involves introducing a vector having the T-type calcium channel nucleic acid into cells of a host in which native expression of the nucleic acid is deficient. Thus, for example, for treating cardiomyopathy associated with deficiencies in T-type calcium channels, the vector is introduced into myocardial cells. Similarly, for treating forms of epilepsy associated with deficiencies in T-type calcium channels, the vector is introduced into neurons (e.g., thalamic neurons). Within the target cells, the nucleic acid within the vector is expressed to produce active T-type calcium channel. By similar methods, an nucleic acid having a sequence antisense to a sequence encoding a T-type calcium channel (or a portion thereof) can be expressed within a cell. The presence of an antisense sequence can down-regulate the expression of native T-type calcium channel genes by hybridizing to T-type channel mRNA within the cell. Thus, the present invention is useful to treating disorders associated with over-expression of T-type calcium channels.

T-type channel proteins (such as whole T-type calcium channels, domains of such channels, chimeras including portions of T-type calcium channels, etc.) can be employed to generate antibodies (e.g., immunoglobulins) to T-type calcium channels. Thus, the present invention provides an isolated and substantially purified antibody molecule recognizing an epitope on a T-type calcium channel. Such antibodies can be monoclonal antibodies or polyclonal antisera. Antibodies recognizing T-type calcium channels can be used to purify the channels from cell extracts or other solutions by standard methodologies (e.g., immunoprecipitation). Moreover, depending on the location of the epitopes for the antibodies on the T-type calcium channel, the antibodies can be used to affect the channel proteins present on the surface of cells. Thus, antibodies directed to T-type calcium channels are potential reagents for studying the channels as well as for therapy.

Such antibodies can be produced by any suitable method, many of which are well known in the art. Thus, for example, the antibodies can comprise polyclonal antisera obtained from innoculated animals. Alternatively, the antibody molecules can be monoclonal antibodies obtained from a cell line (e.g., a hybridoma cell line). Thus,

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the present invention provides a cell which produces such antibodies. Such a cell can be *in vitro* or *in vivo*; however, where the cell is *in vitro*, preferably it is within an established cell line consisting essentially of such cells.

Several examples are presented below to illustrate the invention. Taken together, the examples demonstrate the cloning of twelve novel proteins and their characterization as T-type calcium channel  $\alpha$  subunits. These examples are included here for purely illustrative purposes; as such, they are not to be construed so as to limit the scope of any aspect of the invention.

Many procedures employed in the following examples are techniques routinely performed by one of ordinary skill in the art (see generally Sambrook et al., *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Laboratory. Cold Spring Harbor, NY (1989)) and are not discussed in detail. However, some reagents and methods deserve specific description. Thus, for example, in vitro translation and expression were conducted as described previously (Schneider et al., *Receptors and Channels, 2*, 255-70 (1995)). *Xenopus laevis* oocytes were prepared as described previously (Bernal et al., *J. Pharmacol. Exp. Ther., 282*, 172-80 (1997)). To express proteins, 10 or 30 ng of capped cRNA was injected into the oocytes in a volume of 50 nl. For single channel recording, oocytes were injected with 100 ng capped cRNA and incubated for one week prior to assay.

Cells were voltage clamped using a two-microelectrode voltage clamp amplifier as described (Bernal et al., *J. Pharmacol. Exp. Ther.*, 282, 172-80 (1997)). The standard bath solution contained the following: 40 mM Ba(OH)<sub>2</sub>, 50 mM NaOH, 1 mM KOH, 0.1 mM EDTA, and 5 mM HEPES, adjusted to pH 7.4 with methanesulfonate. The osmolality of the 2 mM Ba<sup>2+</sup> and 10 mM Ba<sup>2+</sup> solutions was balanced by increasing the NaOH concentration as described (Lory et al., *J. Physiol.*, (London), 429, 95-112 (1990)). Voltage and current electrodes (1.5-1.8 M tip resistance) were filled with 3 M KCl. Except as noted, data were acquired at 4 kHz using the pCLAMP system, and filtered at 1 kHz. Data were analyzed using pCLAMP software. Boltzman fits and linear regression were calculated using Prism.

**EXAMPLE 1** 

This example demonstrates the cloning and characterization of putative T-type calcium channels.

A search of the Genbank library was conducted to identify clones identified as having some degree of homology to known calcium channel sequences. The search identified an expressed sequence tagged (EST) partial sequence in a human brain clone (H06096), which was used as a probe to screen a  $\lambda gt10$  cDNA library prepared

from rat brain. Successive screening of the cDNA library identified five overlapping clones which were aligned to construct an entire cDNA sequence, termed  $\alpha 1G$ .

The α1G cDNA was cloned into the pSP72<sup>TM</sup> vector and sequenced by standard computer-assisted sequencing. Using the a1G cDNA, the amino acid 5 sequence of the  $\alpha 1G$  protein was deduced and compared to the sequences of other known calcium channel α subunits. By similar methods, homologous human (H19230 and R19524) and mouse (AA286626) EST clones were also identified and partially sequenced, and alternately spliced variants were identified. The deduced cDNA and amino acid sequences for eight full-length  $\alpha 1G$  T-type channels are set forth, respectively, as SEQ ID NOs:1-8.

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A second T-type calcium channel, termed alH, was isolated by screening a human heart cDNA library with a fragment of the α1G sequence. An alternately spliced isoform was also identified. The full-length cDNA and amino acid sequences for these α1H T-type channels are set forth, respectively, as SEQ ID NOs:9 and 10.

A third T-type calcium channel, termed  $\alpha II$ , was isolated by screening a rat brain cDNA library at low stringency using a fragment of the rat a1G gene. Fifty plaques were identified, many of which were not detected in a second screening. A third screening with a fragment from a1H identified two clones. Subsequent screening, and the use of the GenBank database, led to the identification of the full. length rat and human cDNA and amino acid sequences, set forth at SEQ ID NOs: 11 and 12, respectively.

The  $\alpha$ 1G,  $\alpha$ 1H, and  $\alpha$ 1I amino acid sequences were compared to each other and a known calcium channel ( $\alpha 1E$ ) to investigate the conservation of protein structure and function. The comparison indicates that the  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  amino acid sequences within the putative membrane-spanning domains are about 90 %identical to each other, while the  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  sequences are only roughly 40 % identical to the  $\alpha$ 1E clone.

Figures 1A-1E indicate this conservation between the proteins. The conservation of charged residues, particularly in the S4 domains, is consistent with the role of the α1G, α1H, and α1I proteins as ion channels. However, two of the glutamates associated with ion specificity in other calcium channels have been replaced with aspartate, suggesting altered ion selectivity. Strikingly,  $\alpha 1G$ ,  $\alpha 1H$ , and all display only low homology to sequences linking the membrane-spanning regions within each domain, and even less homology between the intracellular loops linking domains. Notably, neither  $\alpha 1G$ ,  $\alpha 1H$ , nor  $\alpha 1I$  possesses sequences known to bind  $\beta$ subunits or Ca<sup>2+</sup> ions.

#### **EXAMPLE 2**

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This example demonstrates the production of cell lines stably expressing the cloned  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  proteins.

HEK-293 cells were transfected with either the rat α1G cDNA (SEQ ID NO:1), the human α1H cDNA (SEQ ID NO:9), or the rat α1I cDNA (SEQ ID NO:11). As a control, cells were also transfected with human α1E plus human β3 (Schneider et al., Receptors Channels, 2, 255-70 (1994); Murakami et al., Eur. J. Biochem., 236, 138-43 (1996)). The DNA constructs included a neomycin resistance gene conferring resistance to G418. The cells were cultured under standard conditions using medium containing G418 to select for stable transformants.

Surviving clones were expanded and assayed for electrophysiological activity to determine the presence of channels within the membrane. Whole-cell currents were recorded from ruptured patches using an Axopatch 200A amplifier, Digidata 1200 A/D converter, and pCLAMP 6.0 software. Data were digitized at 2 kHz and filtered at 1 kHz or off-line. All experiments were performed at room temperature. Pipettes were made out of TW-150-6 capillary tubing (World Precision Instruments. Inc., Sarasota, FL), using a Model P-97 Flaming-Brown pipette puller (Sutter Instrument Co., Novato, CA). The internal pipette solution contained the following: 55 mM CsCl, 75 mM CsSO<sub>4</sub>, 10 mM MgCl<sub>2</sub>, 0.1 mM EGTA, 10 mM HEPES, pH adjusted to 7.2 with CsOH. The external Tyrodes solution was the following: 140 mM NaCl, 6 mM KCl, 2 mM CaCl<sub>2</sub>, 10 mM glucose, 5 mM HEPES, pH 7.4. The recording solution contained the following: 10 mM BaCl<sub>2</sub> solution (or 2 mM CaCl<sub>2</sub>), 140 mM tetraethylammonium (TEA) chloride, 5 mM CsCl. 1 mM MgCl<sub>2</sub>, 5 mM glucose, and 10 mM HEPES, pH adjusted to 7.4 with TEA-OH. Under these solution conditions the pipette resistance was typically 1.5-2.5  $M\Omega$ . Cell capacitance was measured by integrating the charging current during a 10 mV hyperpolarizing pulse (holding potential -80 mV).

Using these recording techniques, values for pA/pF were obtained for each cell line, which is a measure of current density normalizing for cell size. One clone (#N2) expressed the rat  $\alpha 1G$  protein and has a current density of 42 pA/pF. Another clone (#13), expressed the human  $\alpha 1H$  protein and exhibited a current density of 53 pA/pF. Three clones (#11, #19, and #25) expressed the rat  $\alpha 1I$  protein and exhibited current densities of 40 pA/pF, 45 pA/pF, and 55 pA/pF, respectively

#### 35 EXAMPLE 3

This example demonstrates that the cloned putative T-type calcium channels exhibit T-type current-voltage relationships.

Current traces were elicited by depolarizing voltage clamp pulses of the membranes of cells. The  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  proteins were produced in *Xenopus laevis* oocytes by linearizing the DNA vectors containing the coding sequences, and transcribing the coding sequences *in vitro* by standard methods. Oocytes were then injected with the capped RNA.

Figures 2A-2E depict data obtained from these experiments using cells injected with  $\alpha 1G$  (Figure 2A),  $\alpha 1H$  (Figure 2B), and  $\alpha 1I$  (Figure 2C) and  $\alpha 1E$  (Figure 2D). These data indicate that cells expressing  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  exhibit T-type calcium current, while oocytes expressing  $\alpha 1E$  as well as uninjected oocytes (Figure 6A) do not.

Current voltage curves were developed using cells injected with  $\alpha 1G$ ,  $\alpha 1H$ ,  $\alpha 1I$ , and  $\alpha 1E$ . Figures 3A depicts such data generated in a 10 mM Ba<sup>2+</sup> test solution. These data were transformed into conductance and fit with a Boltzman equation to determine the midpoint of activation ( $V_{0.5}$ ). Gating potentials for  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  (-38 ± 1 mV n=8, -44 mV ± 1 mV, n=10, and -31 mV ± 1 mV, n=6, respectively) were in accordance with the gating potential measured for the HEK-293 cells (-41 ± 1 mV, n=10), while  $\alpha 1E$  required significantly more positive potentials to open (-2.6 mV ± .4 mV, n=3).

To compare the characteristics with published values (Huguenard, Ann. Rev. Physiol., 58, 329-48 (1996)), the  $\alpha$ 1G current was recorded at varying concentrations of Ba<sup>2+</sup>. As indicated in Figure 3B, in solutions containing 2 mM Ba<sup>2+</sup>, V<sub>0.5</sub> was -46.5 mV, and the slope factor (k) was 6.6 (n=7). However, when the Ba<sup>2+</sup> concentration was 40 mM, V<sub>0.5</sub> was recorded at -21 mV, presumably due to the results of barium on surface charge screening (see, e.g., Wilson et al., J. Membrane Biol., 72, 117-30 (1983)). Similar values were recorded for  $\alpha$ 1H and  $\alpha$ 1I.

These results indicate that  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  are low-voltage activated calcium channels (i.e., from about -60 mV to about -30 mV in 10 mM Ba<sup>2+</sup>).

#### **EXAMPLE 4**

This example demonstrates that the cloned putative T-type calcium channels exhibit T-type tail current.

Tail current was measured at -90 mV after first opening the channels with a voltage step to -10 mV. The voltage-dependence of tail current in cells expressing  $\alpha 1G$  (oocytes)  $\alpha 1H$  (HEK 293 cells), and  $\alpha 1I$  (HEK 293 cells) was measured at varying test potentials. As a control, tail current was also measured from a high voltage activated channel  $\alpha 1E$ , which Raw data from recordings data were fit with a single exponential and plotted as a function of depolarization potential (Figure 4).

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These results demonstrate that the tail currents for the cloned  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  calcium channels are voltage-dependent, consistent with known T-type calcium tail currents. Additionally, these data demonstrate that the tail current for each of the cloned channels is between about 1 ms and about 10 ms following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a barium concentration of from about 10 mM to about 40 mM.

#### **EXAMPLE 5**

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This example demonstrates that the cloned putative T-type calcium channels exhibit T-type single channel conductance.

Measurement of single channel conductance is complicated by the low probability of channel opening at negative potentials when the driving force is large. Thus, single channel conductance was measured similarly for measurements of tail currents to enhance channel opening at negative potentials. Single channels were measured with standard depolarizing bath and pipette (115 mM BaCl<sub>2</sub>, 1 mM EGTA, and 10 mM HEPES, pH 7.4) solutions (Lacerda et al., *Biophys. J.*, 66, 1833-43 (1994)). Data were analyzed with TRANSIT (VanDongan, *Biophys J.*, 70, 1303-15 (1996)). Single channel amplitudes were measured by averaging the values obtained from Gaussian fits to all-points histograms of traces with openings, selected openings, or amplitude histograms of idealized openings. It has been reported that some oocytes contain a native 9 pS channel. These endogenous channels can be distinguished by their 2-fold larger current amplitudes at the potentials tested (e.g., -20 mV, i = 0.8 for endogenous channels as opposed to 0.4 pA for  $\alpha$ 1G). However, such endogenous channels were not detected either at the whole cell or single channel level in the oocytes tested.

Current through the main open state of each open channel was measured at each potential and plotted against each test potential. Single channel currents for several patches were then averaged and plotted as a function of test potential, wherein the slope of the plot indicated the single channel conductance. The average slope conductance of the  $\alpha 1G$  channel was measured at  $7.5 \pm 1.5$  pS, which corresponds with the reported values for T-type calcium channels (Hugenard, *Ann. Rev. Phsysiol.*, 58, 329-48 (1996)). Similar results were also obtained with both  $\alpha 1H$  (10.8  $\pm$  1.4 pS). Data collected from recordings of the  $\alpha 1I$  channels indicate that they open to two distinct amplitudes, The conductance for the small amplitude  $\alpha 1I$  openings was measured at  $3.9 \pm 0.5$  pS, while that for the large  $\alpha 1I$  openings was measured at  $11.4 \pm 0.5$  pS).

These results indicate that the cloned  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  proteins exhibit T-type single-channel conductance (e.g., from about 4 to about 12 pS).

#### EXAMPLE 6

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This example demonstrates that a cloned T-type calcium channel can be used for identifying a drug which affects T-type calcium channels.

HEK-293 cells were subjected to treatment as indicated above in Example 3, except that an experimental group of cells were exposed to a solution containing 1  $\mu$ M mibefradil. a known inhibitor of T-type calcium current. As depicted in Figure 5A, the presence of mibefradil almost completely abolished T-type current in cells expressing  $\alpha 1G$ . Cells expressing either  $\alpha 1G$  or  $\alpha 1H$  were similarly treated using various concentrations of mibefradil to determine a dose-response relationship. These results, depicted in Figure 5B, demonstrate that about 50% inhibition was achieved at a mibefradil concentration of 1  $\mu$ M.

All of the references cited herein, including patents, patent applications, and publications, are hereby incorporated in their entireties by reference.

While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations of the preferred embodiments may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.

#### What is claimed is:

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- 1. A isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel  $\alpha$  subunit.
- 2. The nucleic acid of claim 1, wherein said protein comprises an entire T-type calcium channel  $\alpha$  subunit.
- 3. The nucleic acid of claim 2, wherein said protein comprises SEQ ID NO:13.
- 4. The nucleic acid of any of claims 1-3, wherein said calcium channel begins to gate from about -60 mV to about -30 mV in 2 mM Ba<sup>2+</sup>.
- 5. The nucleic acid of any of claims 1-4, wherein said calcium channel exhibits a tail current of from about 1 ms to about 10 ms following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a barium concentration of from about 10 mM to about 40 mM.
- 6. The nucleic acid of any of claims 1-5, wherein said calcium channel exhibits a single channel conductance of from about 4 pS to about 11 pS in a solution with a barium ion concentration of about 100 mM.
  - 7. An isolated or substantially purified nucleic acid hybridizing to the nucleic acid of any of claims 1-6.
  - 8. An isolated or substantially purified nucleic acid hybridizing to the nucleic acid of claim 7.
    - 9. The nucleic acid of claim 8 comprising a sequence encoding at least one domain of a T-type calcium channel  $\alpha$  subunit.
      - 10. A vector comprising the nucleic acid of any of claims 1-9.
      - 11. A cell into which the vector of claim 10 has been introduced.
    - 12. The cell of claim 11, which expresses said nucleic acid to produce said protein.
    - 13. The cell of claim 11 or 12, which stably expresses said nucleic acid to produce said protein.
- 30 14. A population of cells consisting essentially of cells according to any of claims 11-13.
  - 15. An established cell line consisting essentially of cells according to any of claims 11-13.
- 16. A method of identifying a drug which affects T-type calcium channels, said method comprising expressing a T-type calcium channel in a cell, exposing said cell to a putative drug, and measuring the calcium flux through the membrane of said cell in response to a change in membrane potential.

- 17. The method of claim 16, wherein said calcium flux is assayed by using a calcium-sensitive labile dye within said cell.
- 18. The method of claim 16, wherein said calcium flux is assayed by measuring the electrophysiological properties of said cell.
- 19. The method of claim 16. wherein said calcium channel comprises SEQ ID NO:13.
  - 20. An isolated or substantially purified immunoglobulin recognizing an epitope on a T-type calcium channel protein.
    - 21. A cell in vitro which produces the immunoglobulin of claim 20.
- 22. An established cell line consisting essentially of cells according to claim21.

----SFTQLNDLSGAGGRQGPGSTEKDPGSADSEAEGLPYPALAPVVFFYLSQDSRPRSWCLRTVCNPW hCavt2a Mtegaraadevrvplgrrpwpcgvgggvpgeprgagtrggggfelgvspsespaaercaelgadeeorvpypalaatvffclgottrprswclrlvcnpw ----SFWRINDLSGAGGRPGPGSAEKDPGSADSEAEGLPYPALAPVVFFYLSQDSRPRSWCLRTVCNPW ----PAAEPGVTTEQPGPRSPPSSPPGLEEPLDGADPHVPHPDLAPIAFFCLRQTTSPRNWCIKMVCNPW -----APEPG--ITEQPGPRSPPPSPPGLEEPLEGTNPDVPHPDLAPVAFFCLRQTTSPRNWCIKMVCNPW hCavIla MDEEEDGAGAEESGQPR-rCavTla MDEEEDGAGAEESGQPR-MAESASPPSSSAAA---MADSNLPPSSAAAP-hCavT3 rCavT3

FEHVSMLVIMLNCVTLGMFRPCEDVECGSERCNILEAFDAFIFAVEMVIKMYALGLFGQKCYLGDTWNRLDFFIVVAGMÆYSLDGHNVSLSAIRTV FECVSMLVILLNCVTLGMYQPCDDMDCLSDRCKIMQVFDDFIFIFFAMEMVLKMVALGIFGKKCYLGDTWNRLDFFIVMAGMVEYSLDLQNINLSAIRTV FERISMLVILLNCVTLGMFRPCEDIACDSQRCRILQAFDDFIFAFFAVEMVVMVALGIFGKKCYLGDTWNRLDFFIVIAGMLEYSLDLQNVSFSAVRTV rCavtla FERVSMLVILLNCVTLGMFRPCEDIACDSQRCRILQAFDDFIFAFFAVEMVVKMVALGIFGKKCYLGDTWNRLDFFIVIAGMLEYSLDLQNVSFSAVRTV FECVSMLVILLNCVTLGMYQPCDDMECLSDRCKILQVFDDFIFIFFAMEMVLKMVALGIFGKKCYLGDTWNRLDFFIVMAGMVEYSLDLQNINLSAIRTV hCavT1a hCavT2a hCavT3 rCavT3

RVIRPLRAINRVPSMRILVTLLLDTLPMLGNVLLLCFFVFFIFGIVGVQLWAGLLRNRCFLPENFSLPLSVD-LERYYQTENEDESPFICSQPRENGMRS rCavTla RVLRPLRAINRVPSMRILVTLLLDTLPMLGNVLLLCFFVFFIFGIVGVQLWAGLLRNRCFLPENFSLPLSVD-LEPYYQTENEDESPFICSQPRENGMRS hCavT2a RVLRPLRAINRVPSMRILVTLLLDTLPMLGNVLLLCFFVFFIFGIVGVQLWAGLLRNRCFLDSAFVRNNNLTFLRPYYQTEEGEENPFICSSRRDNGMOK RVLRPLKAINRVPSMRILVNLLLDTLPMLGNVLLLCFFVFFIFGIIGVQLWAGLLRNRCFLEENFTIQGDVA-LPPYYQPEEDDEMPFICSLSGDNGIMG RVLRPLKAINRVPSMRILVNLLLDTLPMLGNVLLLCFFVFFIFGIIGVQLWAGLLRNRCFLEENFTIQGDVA-LPPYYQPEEDDEMPFICSLTGDNGIMG hCavTla hCavT3 rCavT3

hCavTla CRSVPTLRGDG-----GGGPPCGLDYEAYNSSSNTTCVNWNQYYTNCSAGEHNPFKGAINFDNIGYAWIAIFQVITLEGWVDIMYFVMDAHSFYNFIYFI rcavīla crsvpīlrgeg-----gggppcsldyetynsssnītcvnmnqyyīncsagehnpēkgainednigyawiaieqvitlegwvdimyfvmdahsfynfiyfī hCavT2a CSHIPGRRDVRMPCTLGWEA-YTQPQAEGVGAARNACINWNQYYNVCRSGDSNPHNGAINFDNTCYAWIAIFQVITLEGWVDIMYYVMDAHSFYNFIYFI CHEIPPLKEQGRECCLSKODVYDFGAGRODLNASGLCVNWNRYYNVCRTGSANPHKGAINFDNIGYAWIVIFQVITLEGWVEIMYYVMDAHSFYNFIYFI CHEIPPLKEQGRECCLSKODVYDFGAGRQDLNASGLCVNWNRYYNVCRTGNANPHKGAINFDNIGYAGIVIFQVITLEGWVEIMYYVMDAHSFYNFIYFI IP LOOP hCavT3 rCavT3

rcavīla llingsffminlcinviatgfsetkoresolmreorvrflsnastlasfsepgscyeellkylvyilrkaarrlaqusraigvragilsspvarsgoep hCavT2a LLIIVGSFFMINLCLVVIATQFSETKQRESQLMREQRARHLSNDSTLASFSEPGSCYEELLKYVGHIFRKVKRRSLRLYARWQSRWRKKVDPSAVQGQGP hcavtla illivgsffminicivviatofsetkoresolmreorvflsnastlasfsepgscyeelikylvyilrkaarrlaovsraagvrvgllsspapiggoet hCavt3 lliivgsffminiclvviatofsetkorehrimleororylss-stvasyaepgdcyeeifoyvchilrkakrralglyqalqsrro-------LLIIVGSFFMINLCLVVIATQFSETKQREHRLMLEQRQRYLSS-STVASYAEPGDCYEEIFQYVCHILRKAKRRALGLYQALQNRRQ---rCavT3

Fig. 1A

hCavTla IAILVNTLSMGIEYHEQPEELTNALEISNIVFTSLFALEMLLKLLVYGPFGYIKNPYNIFDGVIVVISVWEIVGQQGGGLSVLRTFRLMRVLKLVRFLPA rcavīla iailvnīlsmgieyheqpeeltnaleisnivfīslfalemliklivygpfgyiknpynifdgvivvisvweivgooggglsvlrtfrimrvlklvrfipa hCavt2a MAILVNTLSMGVEYHEQPEELTNALEISNIVFTSMFALEMLLKLLACGPLGYIRNPYNIFDGIIVVISVWEIVGQADGGLSVLRTFRLLRVLKLVRFLPA

mailvntvsmgiehheopeeltnileicnvvftsmfalemilklaafglfdylrnpynifdsiiviisiweivgoadgglsvlrtfrllrvlklvrfmpa MAILVNTVSMGIEHHEQPEELTNILEICNVVFTSMFALEMILKLAAFGLFDYLRNPYNIFDSIIVIISIWEIVGQADGGLSVLRTFRLLRVLKLVRFMPA

hCavT3

rCav13

hCavTla LORQLVVIMKTMDNVATFCMLIMLFIFIFSILGMHLFGCKFASERD-GDTLPDRKNFDSLLWAIVTVFQILTQEDWNKVLYNGMASTSSWAALYFIALMT rcavīla lorolivylmkīmdnvaffcmlimleifiesilcmhlfgckfaserd-gdtlpdrknfdslimaivīvfgiltoedmnkvlyncmastsswaalyfialmī hCavT2a LRRQLVVLVKTMDNVATFCTLLMLFIFIFSILGMHLFGCKFSLKTDTGDTVPDRKNFDSLLWAIVTVFQILTQEDWNVVLYNGMASTSSWAALYFVALMT

IIP LOOP

hCavT2a GHRQRRAGRHTASVHHLVYHHHHHHHHHHYHFSHGSPRRPGPEPGACDTRLVRAGAPPSPPSPGRGPPDAESVHSIYHADCHIEGPQERARVGTCRSHCRC rcavila Qappprcpseasgrivgsgkvypivhispppeilkokalvevapspgppilisen-ippgpfssmhklleiqsigachssckisspcskadsgacgpdsc hCavI2a QPQAGHRAGHHELPHDPALRGGQRQRQRQPRIQGEVGRWTARHRGHGPLSLNSPDPYEKIPHVAGEHGLGQAPGHLSGLSVPCPLPSPPAGTLTCELKSC -----ALGPEAPARARPGPHAKEPRHYQLCPQHSPLDATPHTLVQPIPATLASDPASC -----AMGPGTPAPAKPGPHAKEPSHCKLCPRHSPLDPTPHTLVQPISAILASDPSSC rcavila pycari-gagepesadhvmpdsdseavyeftqdaqhsdlrdphs-------rrrqrslgpdaepssvlafwrlicdifrkivdskyfgrgim PYCTRALEDPEGELSGSESGDSDGRGVYEFTQDVRHGDRWDPTRPPRATDTPGPGSPQRRAQQRAAPGEPGWMGRLWVTFSGKLRRIVDSKYFSRGIM PCCQHEDGRRPSGLGSTDSGQEGS-----GSGSSAGGEDEADGDGARSSEDGASSELGKEEEEEEQADGAVWLCGDVWRETRAKLRGIVDSKYFNRGIM --ESVHSFYHADCHLEPVRC ----ESVHSFYHADCHLEPVRC hCavila Qappprspseasgrivgsgkvyptvhtspppetlkekalvevaassgppilisln-Ippgpyssmhklletqstgacqssckisspclkadsgacgpdsc ----RR-QRSLGPDAEPSSVLAFWRLICDTFRKIVDSKYFGRGIM PHCQHEAGRRPSGLGSTDSGQEGS-----GSGGSA--EAEANGDGLQSSEDGVSSDLGKEEEQE----DGAARLCGDVWRETRKKLRGIVDSKYFNRGIM rCavtla QPSGSCTRSHRRLSVHHLVHHHHHHHHHYHLGNGTLRVPRASPEIQDRDANGSRRLMLPPPSTPTPSGGPPRGA---hCavtla QPSSSCSRSHRRLSVHHLVHHHHHHHHHYHLGNGTLRAPRASPEIQDRDANGSRRLMLPPPSTPALSGAPPGGAhCavIla PYCARA-GAGEVELADREMPDSDSEAVYEFTQDAQHSDLRDPHS--hCavT2a hCavT3 rCavT3 rCavT3 hCavT3 hCavT3 rCavT3

Fig. 1B

LRROLVVIMKTMDNVATFCMLIMLFIFIFSILGMHIFGCKFSLRTDTGDTVPDRKNFDSLLMAIVTVFQILTQEDWNVVLYNGMASTSPWASLYFVALMT LRRQLVVIMKTMDNVATFCMLLMLFIFIFSILGMHIFGCKFSLRTDTGDTVPDRKNFDSLLMAIVTVFQILTQEDMNVVLYNGMASTTFWASLYFVALMT

hCavT3

rCavT3

hCavt2a fgnyvlenllvailvegfqaegdanrsdtdedktsvhfeedfhklrelqttelkmcslavtpngtwrdeaacplpsscaqlprpclpprahhswmqppas FGNYVLFNLLVAILVEGFQAEGDANKSESEPDFFSPSLDGDGDRKKCLALVSLGEHPELRKSLLPPL----IIHTAATPMSLPKSTSTGLGEALGPASR FGNYVLFNLLVAILVEGFQAEGDATKSESEPDFFSPSVDGDGDRKKRLALVALGEHAELRKSLLPPL----IIHTAATPMSHPKSSSTGVGEALGSGSR FGNYVLFNLLVAILVEGFQAEGDANRSYSDEDQSSSNIEEFDKLQEGLDSSGDPKLCPIPMTPNGHLDPSLPLGGHLGPAGAAGPAPRLSLQPDPMLVAL FGNYVLFNLLVAI LVEGFQAEGDANRSCSDEDQSSSNLEEFDKLPEGLDNSRDLKLCP I PMTPNGHLDPSLPLGAHLGPAGTMGTAPRLSLQPDPVLVAL rCavIla hCavT3 rCavT3

----SPSGERRSLLSGEGQESQDEEESSEEERASP rcavtla Rtsssgsaepgaahhemkcppsarssphspwsaasswtsrrssrnslgrapslkrr------spsgerrsllsgeggesqdeeesseedrasp -----PACQCGERESILSGEGKGSTDDEAEDGRARS GSRKSSVMSLGRMSYDQRSLSSSRSSYYGPWGRSAAWASRRSSWNSLKHKPPSAEHESLLSAERGGG-ARVCEVAADEGPPRAAPLHTPHAHHVHHGPHL DSRKSSVMSLGRMSYDQRSLSSSRSSYYGPWGRSGTWASRRSSWNSLKHKPPSAEHESLLSGEGGGGCVRACEGAREEAPTRTAPLHAPHAHHGPHL nCavIla RISSSGSAEPGAAH-EMKSPPSARSSPHSPWSAASSWISRRSSRNSLGRAPSLKRR----hCav12a QTLGVAAAAPGTRHWETRSLRQPPKFSLCPLGPSGAWSSRRSSWSSLGRAQPQA---hCavT3 rCavT3

rCavTla AGSDHRHRGSLEREAKSSFDLPDTLQVPGLHRTASGRSSASEH--QDCNGKSASGRLARTLRTDDPQLDGDDDNDEGNLSKGERIQAWVRSRLPACCRERD hCavTla AGSDHRHRGSLEREAKSSFDLPDTLQVPGLHRTASGRGSASEH--QDCNGKSASGRLARALRPDDPPLDGDDADDEGNLSKGERVRAWIRARLPACCLERD hCavT2a GPRATPLRRAESLDPR----------PLRRPPPAYQVRDRDGQVVALPSDFFLRIDSHREDAAELDDDSEDSCCLRLHKVLVPYKPQRCRSRRPG AHRHRHHRRTLSLDTRDSVDLGELVPVVGAHSRAAWRGAGQAPGHEDCNGRMPNIAKDVFTKMDDRRDRGEDEEEIDYTLCFRVRKMIDVYKPDWCEVRE AHRHRHHRRTLSLDNRDSVDLAELVPAVGAHPRAAWRAAGPAPGHEDCNGRMPSIAKDVFTKMGDRGDRGDEEEIDYTLCFRVRKMIDVYKPDWCEVRE hCavT3 rCavT3

hCavT2a PSTLYLFSPQNRFRVSCQKVITHKMFDHVVLVFIFLNCVTIALERPDIDPGSTERVFLSVSNYIFTAIFVAEMMVKVVALGLLSGEHAYLQSSWNLLDGL DWSVYLESPENRFRVLCQTI IAHKLFDYVVLAFIFLNCITIALERPQIEAGSTERIFLTVSNYIFTAIFVGEMTLKVVSLGLYFGEQAYLRSSWNVLDGF hCavTla SWSAYIFPPQSRFRLLCHRIITHKWFDHVVLVIIIFLNCITIAMERPKIDPHSAERIFLTLSNYIFTAVFLAEMTVKVVALGWCFGEQAYLRSSWNVLDGL rcavtla swsayifppqsrfrllchriithkwfdhvvlviiflncitiamerpkidphsaerifltlsnyiftavflæmtvkvvalgwcfgeqaylrsswnvldgl DWSVYLESPENKFRILCQTIIAHKLFDYVVLAFIFINCITIALERPQIEAGSTERIFLTVSNYIFTAIFVGEMTLKVVSLGLYFGEQAYLRSSWNVLDGF IIII hCavT3 rCavT3

hCavtla LVLISVIDILVSMVSDSGTKILGMLRVLRLLRTLRPLRVISRAQGLKLVVETLMSSLKPIGNIVVICCAFFIIFGILGVQLFKGKFFVCQGEDTRNITNK rCavTla LVLISVIDILVSMVSDSGTKILGMLRVLRLIRTLRPLRVISRAQGLKLVVETLMSSLKPIGNIVVICCAFFIIFGILGVQLFKGKFFVCQGEDTRNITNK hCavT2a LVLVSLVDIVVAMASAGGAKILGVLRVLRLLRTLRPLRVISRAPGLKLVVETLISSLRPIGNIVLICCAFFIIFGILGVQLFKGKFYYCEGPDTRNISTK LVFVSIIDIVVSLASAGGAKILGVLRVLRLLRTLRPLRVISRAPGLKLVVETLISSLKPIGNIVLICCAFFIIFGILGVQLFKGKFYHCLGVDTRNITNR LVFVSIIDIVVSVASAGGAKILGVLRVLRLLRTLRPLRVISRAPGLKLVVETLISSLKPIGNIVLICCAFFIIFGILGVQLFKGKFYHCLGVDTRNITNR IIIS4 rCavT3

hCavT1a

IIIP LOOP

hCavTla SDCAEASYRWVRHKYNFDNLGQALMSLFVLASKDGWVDIMYDGLDAVGVDQQPIMNHNPWMLLYFISFLLIVAFFVLNMFVGVVVENFHKCRQHQEEEEA rcavtla SDCAEASYRWVRHKYNFDNLGQALMSLFVLASKDGWVDIMYDGLDAVGVDQQPIMNHNPWMLLYFISFLLIVAFFVLNMFVGVVVENFHKCRQHQEEEEA hCavīza AQCRAAHYRWVRKYNFDNLGQALMSLFVLSSKDGWVNIMYDGLDAVGVDQQPVQNHNPWMLLYFISFLLIVSFFVLNMFVGVVVENFHKCRPHQEAEEA SDCMAANYRWVHHKYNFDNLGQALMSLFVLASKDGWVNIMYNGLDAVAVDQQFVTNHNPWMLLYFISFLLIVSFFVLNMFVGVVVENFHKCRQHQEAEEA SDCVAANYRWVHHKYNFDNLGQALMSLFVLASKDGWVNIMYNGLDAVAVDQQPVTNHNPWMLLYFISFLLIVSFFVLNMFVGVVVENFHKCRQHQEAEEA hCavT3 rCavT3

hCavTla RRREEKRLRRLEKKRRSKEKQMAEAQCKPYYSDYSRFRLLVHHLCTSHYLDLFITGVIGLNVVTWAMEHYQQPQILDEALKICNYIFTVIFVLESVFKLV fCavIla RRREEKRIRRIEKKRRSKEKQMAEAQCKPYYSDYSRFRLLVHHLCTSHYLDLFITGVIGLNVVTMAMEHYQQPQILDEALKICNYIFTVIFVFESVFKLV hCav12a RRREEKRLRRLERRR-STFPSPEAQRRPYYADYSPTRRWIHSLCTSHYLDLFITFIICVNVITMSMEHYNQPKSLDEALKYCNYVFTIVFVFEAALKLV hcavī3 RRREEKRLRRLEKKRR-K-----AQRLPYYATYCHTRLLIHSMCTSHYLDIFITFIICLNVVTMSLEHYNQPTSLETALKYCNYMFTTVFVLEAVLKLV RREEKRLRLEKKRR-K-----AQRLPYYATYCPTRLLIHSMCTSHYLDIFITFIICLNVVTMSLEHYNQPTSLETALKYCNYMFTTVFVLEAVLKLV rCavT3

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hCavIla LFGDLECDETHPCEGLGRHATFRNFGMAFLTLFRVSTGDNWNGIMKDTLRDCDQEST---CYNTVISPIYFVSFVLTAQFVLVNVVIAVIMKHLEESNKE rCavīla LFGDLECDETHPCEGLGRHATFRNFGMAFLTLFRVSTGDNWNGIMKDTLRDCDQEST---CYNTVISPIYFVSFVLTAQFVLVNVVIAVIMKHLEESNKE hCavT2a LFGRLECSEDNPCEGLSRHATFSNFGMAFLTLFRVSTGDNWNGIMKDTLRECSREDKHCLSYLPAPSPVYFVTFVLVPQFVLVNVVVAVIMKHLEESNKE LFGKLVCNDENPCEGMSRHATFENFGMAFLTLFQVSTGDNWNGIMKDTLRDCTHDERSCLSSLQFVSPLYFVSFVLTAQFVLINVVVAVLMKHLDDSNKE LFGKLVCNDENPCEGMSRHATFENFGMAFLTLFQVSTGDNWNGIMKDTLRDCTHDERTCLSSLQFVSPLYFVSFVLTAQFVLINVVVAVIMKHLDDSNKE IVP LOOP hCavT3 rCavT3

hCavTla AKEEAELEAELELEMKTLSPQPHSPLGSPFLWPGVEGPDSPDSPKPGALHPAAHARSASHFSLEHPTMQPHPTELP---GPDLLTVRKSGVSRTHSLPND rcavtla akeeaeleaelelemktlspophsplgspflwpgvegvnstdspkpgaphttahigaasgfslehptwvphpeevpvplgpdlltvrksgvsrthslpnd hCavT2a AREDAEIDAEIELEMAQGPGSARRV---------------------------DADRPPLPQESPGARDAPNIVARKVSVSRMLSLPND AQEDAEMDAE IELEMAHGLGPCPGPCPCPCPCPCPCA------hCavT3 rCavT3

Fig. 1D

hCa,Tla rCa,Tla hCa,T2a hCa,T3 rCa,T3	hCa,Tla SYMCRHGSTAEGPLGHRGWGLPKAQSGSVLSVHSQPADTSYILQLPKDAPHLLQPHSAPTWGTIPKLPPFGKSPLAQKPLKKQAAIKTDSLDVQGLGSKE rCa,Tla SYMCRNGSTAERSLGHRGWGLPKAQSGSILSVHSQPADTSCILQLPKDPHGAPTWGAIPKLPPPGRSPLAQRPLRRQAAIRTDSLDVQGLGSKE hCa,T2a SYMFRPVVPASAPHPRPLQEVEMETYGAGTPLGSVASVHSPPAESCASLQIPLAVSSPARSGE
hCavila rCavila hCavila hCavila rCavil	hca,Tia dilaevsgpspplaraysewggsstgagghsrshskiskhmtppapcpgpepnwgkgppeikssleldtelswisgdllppggesppplkkcisve rca,Tia dilsevsgpscpltrsssfwggssigvggrsgigskvskhirlpapcpglepswakdppetrssleldtelswisgdllpss-geeplfprdikkcysve hca,T2a
hCa <sub>v</sub> Tla	hcavtla agscorrptswideorrhsiavscidsgsophigtdpsniggopiggpgsrpkkkisppsitidppesogsrippspgicirrrapssdskopiasgppd
rCa <sub>v</sub> Tla	FCavtla toscrrrpgfwideorrhsiavscidsgsopricpspssiggopiggpgsrpkkkisppsisidppesogsrppcspgvcirrrapasdskoppsvsspid
hCa,Tla	hCa,Tla SMAASPSPKKOVLSLSGLSSDPADLDP (SEQ ID NO:1)
rCa,Tla	rCa,Tla STAASPSPKKOTLSLSGLSSDPTDMDP (SEQ ID NO:5)

F18. 1E

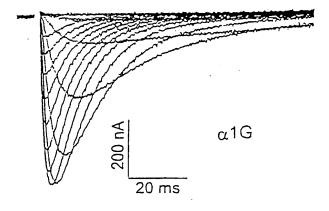


Figure 2A

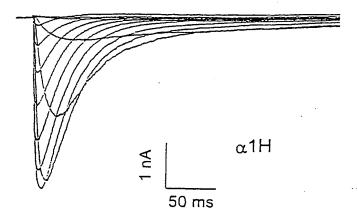


Figure 2B

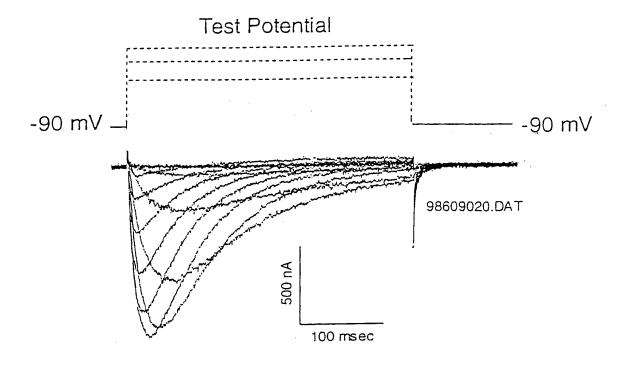


Figure 2C

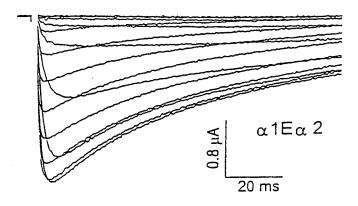


Figure 2D

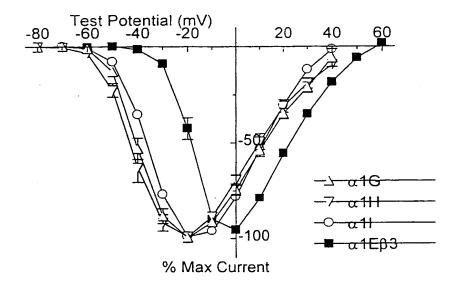


Figure 3A

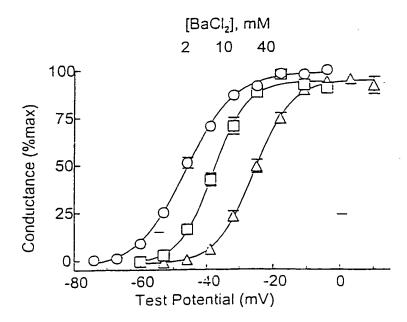


Figure 3B

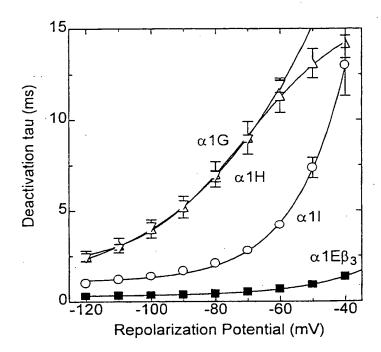


Figure 4

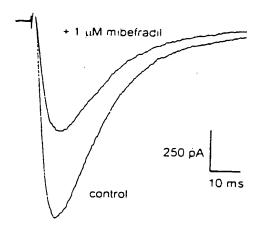


Figure 5A

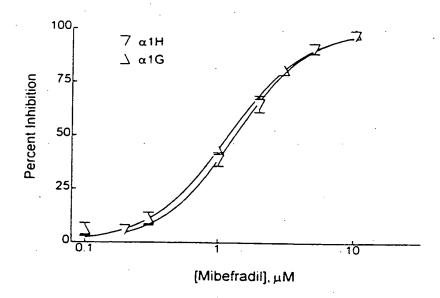


Figure 5B

#### SEQUENCE LISTING

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45	gag go Glu Gl	gg ctg Ly Leu 50	ccg Pro	tac Tyr	ccg Pro	gcg Ala 55	ctg Leu	gcc Ala	ccg Pro	gtg Val	gtt Val 60	ttc Phe	ttc Phe	tac Tyr	ttg Leu	192
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45	tac Tyr 305	aac Asn	agc Ser	tcc Ser	agc Ser	aac Asn 310	acc Thr	acc Thr	tgt Cys	gtc Val	aac Asn 315	tgg Trp	aac Asn	cag Gln	tac Tyr	tac Tyr 320	960
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WO 99/29847 PCT/US98/23161

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15	gac Asp	agc Ser 690	gag Glu	gca Ala	gtt Val	tat Tyr	gag Glu 695	ttc Phe	aca Thr	cag Gln	gat Asp	gcc Ala 700	cag Gln	cac His	agc Ser	gac Asp	2112
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40	ggc Gly	tac Tyr	atc Ile	aag Lys	aat Asn 805	ccc Pro	tac Tyr	aac Asn	atc Ile	ttc Phe 810	gat Asp	ggt Gly	gtc Val	att Ile	gtg Val 815	gtc Val	2448
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	Gly	Asp	Thr	900	Pro	Asp	Arg	g Lys	905	Phe	e Asp	o Ser	Let	Let 910		) Ala	
5	atc Ile	gto Val	act Thr 915	· Val	ttt Phe	cag Gln	ato	ctg Leu 920	Thr	cag Gln	gaç Glu	g gac 1 Asp	tgc Trp 925	Asr	aaa Lys	gtc Val	2784
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	cct Pro	gcg Ala	tcg Ser	Arg	cgc Arg 1045	acc Thr	agc Ser	agc Ser	Ser	ggg. Gly L050	tcg Ser	gca Ala	gag Glu	Pro	ggg Gly 1055	ġcg Ala	3168
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	gac .	aça	ctg.	cag	gtg	cca	ggg	ctg	cat	cgc	act	gcc	agt	ggc ggc	cga	ggg .	3504

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	Ala S∈ 1665	∍r Leu	Pro	Ile	Asn 1670	.Pro	Thr	Ile		Arg 1675		Met	Arg	. Val	Leu 1680	
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	ctg ga Leu Gl 189	u Hıs	ccc Pro	acg Thr	Met	cag Gln 895	ccc Pro	cac His	ccc Pro	Thr	gag Glu 900	ctg Leu	cca Pro	gga Gly	cca Pro	5712
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	ccc aa	t gac	agc	tac	atg	tgt	cgg	cat	ggg	agc.	act	gcc	gag	ggg	ccc	5808

	Pro Asn Asp Ser Tyr Met Cys Arg His Gly Ser Thr Ala Glu Gly Pro 1925 1930 1935	
5	ctg gga cac agg ggc tgg ggg ctc ccc aaa gct cag tca ggc tcc gtc Leu Gly His Arg Gly Trp Gly Leu Pro Lys Ala Gln Ser Gly Ser Val 1940 1945 1950	5556
10	ttg tcc gtt cac tcc cag cca gca gat acc agc tac atc ctg cag ctt Leu Ser Val His Ser Gln Pro Ala Asp Thr Ser Tyr Ile Leu Gln Leu 1955 1960 1965	5904
15	ccc aaa gat gca cct cat ctg ctc cag ccc cac agc gcc cca acc tgg Pro Lys Asp Ala Pro His Leu Leu Gln Pro His Ser Ala Pro Thr Trp 1970 1975 1980	5952
	ggc acc atc ccc aaa ctg ccc cca cca gga cgc tcc cct ttg gct cag Gly Thr Ile Pro Lys Leu Pro Pro Gly Arg Ser Pro Leu Ala Gln 1985 1990 1995 2000	6000
20	agg cca ctc agg cgc cag gca gca ata agg act gac tcc ttg gac gtt Arg Pro Leu Arg Arg Gln Ala Ala Ile Arg Thr Asp Ser Leu Asp Val 2005 2010 2015	6048
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<i>30</i> .	too cog coo ctg goo cgg goo tao tot tto tgg ggo cag toa agt aco Ser Pro Pro Leu Ala Arg Ala Tyr Ser Phe Trp Gly Gln Ser Ser Thr 2035 2040 2045	6144
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	Lys Lys Le	eu Ser Pro 2180	Pro Ser		Thr Ile 185	Asp Pro	Pro Glu 2190	Ser Gln	
5	ggt cct cc Gly Pro Ar 219	g Thr Pro	ccc ago Pro Ser	c cct c Pro 0 2200	ggt atc Gly Ile	Cys Leu	cgg agg Arg Arg 2205	agg get Arg Ala	6624.
10	ccg tcc ac Pro Ser Se 2210	ge gae tee er Asp Ser	aag gat Lys Asp 2215	Pro I	tg gcc Leu Ala	tct ggc Ser Gly 2220	ccc cct Pro Pro	gac agc Asp Ser	6672
15	atg gct gc Met Ala Al 2225	c tog cod a Ser Pro	tcc cca Ser Pro 2230	aag a Lys I	Lys Asp	gtg ctg Val Leu 235	agt ctc Ser Leu	tcc ggt Ser Gly 2240	6720
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25	<211> 6783 <212> DNA <213> Homo				-				
23	<220> <221> CDS <222> (1).	. (6783)							
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40	ggg ccg gg Gly Pro Gl 3	g tca gca y Ser Ala 5	gaa aag Glu Lys	gac c Asp P 40	ccg ggc Pro Gly	agc gcg Ser Ala	gac tcc Asp Ser 45	gag gcg Glu Ala	.144
45	gag ggg ct Glu Gly Le 50	g ccg tac u Pro Tyr	ccg gcg Pro Ala 55	Leu A	jcc ccg Ala Pro	gtg gtt Val Val 60	ttc ttc Phe Phe	tac ttg Tyr Leu	192
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	ccc tgg tt Pro Trp Ph	t gag cgc e Glu Arg 85	Ile Ser	atg t Met L	tg gtc Leu Val 90	atc ctt Ile Leu	ctc aac Leu Asn	tgc gtg Cys Val 95	288
<i>55</i>	acc ctg gg Thr Leu Gl	y Met Phe	cgg cca Arg Pro	Cys G	gag gac Slu Asp 105	atc gcc Ile Ala	tgt gac Cys Asp 110	tcc cag Ser Gln	336
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	gcc gtg ga Ala Val Gl	g atg gtg u Met Val	gtg aag Val Lys	atg g Met V	gtg gcc /al Ala	ttg ggc Leu Gly	atc ttt Ile Phe	ggg aaa Gly Lys	432

		130					135	5				140	)				
5	aag Lys 145	у Суз	tac Tyr	cto Lei	g gga ı Gly	gac Asp 150	Thr	tgç Trp	j aac O Asr	c cgg	g ctt J Leu 155	ı Asr	ttt Phe	tto Phe	ato Elle	gtc Val 160	480
10	ato Ile	gca Ala	ggg Gly	y ato Met	t Ctg Leu 165	GIU	tac Tyr	tcg Ser	ctg Leu	gac Asp 170	, Lei	g caç i Gln	aac Asr	gtc Val	ago Ser 175	ttc Phe	528
	tca Ser	gct Ala	gto Val	agg Arg 180	Inr	gtc Val	cgt Arg	gtg Val	ctg Leu 185	. Arg	ccç Pro	cto Leu	agg Arg	gcc Ala 190	Ile	aac Asn	576
15	cgg Arg	gtg Val	Pro 195	Ser	atg Met	cgc Arg	atc Ile	ctt Leu 200	gtc Val	acg Thr	ttg Leu	ctg Leu	ctg Leu 205	Asp	acg Thr	ctg Leu	624
20	ccc Pro	atg Met 210	Leu	ggc Gly	aac Asn	gtc Val	ctg Leu 215	ctg Leu	ctc Leu	tgc Cys	ttc Phe	ttc Phe 220	Val	ttc Phe	ttc Phe	atc Ile	672
25	ttc Phe 225	ggc Gly	atc Ile	gtc Val	ggc Gly	gtc Val 230	cag Gln	ctg Leu	tgg Trp	gca Ala	ggg Gly 235	Leu	ctt Leu	cgg Arg	aac Asn	cgā Arg 240	720
30	tgc Cys	ttc Phe	cta Leu	cct Pro	gag Glu 245	aat Asn	ttc Phe	agc Ser	ctc Leu	ccc Pro 250	ctg Leu	agc Ser	gtg Val	gac Asp	ctg Leu 255	gag Glu	768
	cgc Arg	tat Tyr	tac Tyr	cag Gln 260	aca Thr	gag Glu	aac Asn	gag Glu	gat Asp 265	gag Glu	ag <u>c</u> Ser	ccc Pro	ttc Phe	atc Ile 270	tgc Cys	tcc Ser	816
35	cag Gln	cca Pro	cgc Arg 275	gag Glu	aac Asn	ggc Gly	atg Met	cgg Arg 280	tcc Ser	tgc Cys	aga Arg	agc Ser	gtg Val 285	ccc Pro	acg Thr	ctg Leu	864
40	cgc Arg	ggg Gly 290	gac Asp	ggg Gly	ggc Gly	ggt Gly	ggc Gly 295	cca Pro	cct Pro	tgc Cys	ggt Gly	ctg Leu 300	gac Asp	tat Tyr	gag Glu	gcc Ala	912
45	tac Tyr 305	ASII	agc Ser	tcc Ser	agc Ser	aac Asn 310	acc Thr	acc Thr	tgt Cys	gtc Val	aac Asn 315	tgg Trp	aac Asn	cag Gln	tac Tyr	tac Tyr 320	960
50	acc Thr	aac Asn	tgc Cys	tca Ser	gcg Ala 325	ggg Gly	gag Glu	cac His	aac Asn	ccc Pro 330	ttc Phe	aag Lys	ggc Gly	gcc Ala	atc Ile 335	aac Asn	1008
	ttt Phe	gac Asp	aac Asn	att Ile 340	ggc Gly	tat Tyr	gcc Ala	tgg Trp	atc Ile 345	gcc Ala	atc Ile	ttc Phe	cag Gln	gtc Val 350	atc Ile	acg Thr	1056
<i>55</i>	ctg Leu	gag Glu	ggc Gly 355	tgg Trp	gtc Val	gac Asp	TTE	atg Met 360	tac Tyr	ttt Phe	gtg Val	atg Met	gat Asp 365	gct Ala	cat His	tcc Ser	1104 -
60	ttc Phe	tac Tyr 370	aat Asn	ttc Phe	atc Ile	tac Tyr	ttc Phe 375	atc Ile	ctc Leu	ctc Leu	atc Ile	atc Ile 380	gtg Val	ggc Gly	tcc Ser	ttc Phe	1152
	ttc Phe	atg Met	atc Ile	aac Asn	ctg Leu	tgc Cys	ctg Leu	gtg Val	gtg Val	att Ile	gcc Ala	acg Thr	cag Gln	ttc Phe	tca Ser	gag Glu	1200

	385					390					395					400	
5	acc Thr	aag Lys	cag Gln	Arg	gaa Glu 405	agc Ser	cag Gln	ctg Leu	atg Met	cgg Arg 410	gag Glu	cag Gln	cgt Arg	gtg Val	cgg Arg 415	ttc Phe	1248
10	ctg Leu	tcc Ser	Asn	gcc Ala 420	Ser	acc Thr	ctg Leu	gct Ala	agc Ser 425	ttc Phe	tct Ser	gag Glu	ccc Pro	ggc Gly 430	Ser	tgc Cys	1296
	tat Tyr	gag Glu	gag Glu 435	ctg Leu	ctc Leu	aag Lys	tac Tyr	ctg Leu 440	Val	tac Tyr	atc Ile	ctt Leu	cgt Arg 445	aag Lys	gca Ala	gcc Ala	1344
15	cgc Arg	agg Arg 450	ctg Leu	gct Ala	cag Gln	gtc Val	tct Ser 455	cgg Arg	gca Ala	gca Ala	ggt Gly	gtg Val 460	cgg Arg	gtt Val	Gly ggg	ctg Leu	1392
20	ctc Leu 465	agc Ser	agc Ser	cca Pro	gca Ala	ccc Pro 470	ctc Leu	Gly Ggg	ggc Gly	cag Gln	gaģ Glu 475	acc Thr	cag Gln	ccc Pro	agc Ser	agc Ser 480	1440
25	agc Ser	tgc Cys	tct Ser	cgc Arg	tcc Ser 485	cac His	cgc Arg	cgc Arg	cta Leu	tcc Ser 490	gtc Val	cac His	cac Hís	ctg Leu	gtg Val 495	cac His	1,488
30	cac His	cac His	cac His	cac His 500	cat His	cac His	cac His	cac His	tac Tyr 505	cac His	ctg Leu	ggc Gly	aat Asn	999 Gly 510	acg Thr	ctc Leu	1536
	agg Arg	gcc Ala	ccc Pro 515	cgg Arg	gcc Ala	agc Ser	ccg Pro	gag Glu 520	atc Ile	cag Gln	gac Asp	agg Arg	gat Asp 525	gcc Ala	aat Asn	ggg Gly	1584
35	tcc Ser	cgc Arg 530	cgg Arg	ctc Leu	atg Met	ctg Leu	cca Pro 535	cca Pro	ccc Pro	tcg Ser	acg Thr	cct Pro 540	gcc Ala	ctc Leu	tcc Ser	Gly ggg	1632
40	gcc Ala 545	ccc Pro	cct Pro	ggt Gly	ggc Gly	gca Ala 550	gag Glu	tct Ser	gtg Val	cac His	agc Ser 555	ttc Phe	tac Tyr	cat His	gcc Ala	gac Asp 560	··1680
45	tgc Cys	cac His	tta Leu	gag Glu	cca Pro 565	gtc Val	cgc Arg	tgc Cys	cag Gln	gcg Ala 570	ccc Pro	cct Pro	ccc Pro	agg Arg	tcc Ser 575	cca Pro	1728
50	tct Ser	gag Glu	gca Ala	tcc Ser 580	ggc Gly	agg Arg	act Thr	gtg Val	ggc Gly 585	agc Ser	ggg Gly	aag Lys	gtg Val	tat Tyr 590	ccc Pro	acc Thr	1776
	gtg Val	cac His	acc Thr 595	agc Ser	cct Pro	cca Pro	ccg Pro	gag Glu 600	acg Thr	ctg Leu	aag Lys	gag Glu	aag Lys 605	gca Ala	cta Leu	gta Val	1824
<i>55</i>	gag Glu	gtg Val 610	gct Ala	gcc Ala	agc Ser	tct Ser	ggg Gly 615	ccc Pro	cca Pro	acc Thr	ctc Leu	acc Thr 620	agc Ser	ctc Leu	aac Asn	atc Ile	1872
60	cca Pro 625	ccc Pro	ggg Gly	ccc Pro	tac Tyr	agc Ser 630	tcc Ser	atg Met	cac His	aag Lys	ctg Leu 635	ctg Leu	gag Glu	aca Thr	ca`g Gln	agt Ser 640	1920
	aca Thr	ggt Gly	gcc Ala	tgc Cys	caa Gln	agc Ser	tct Ser	tgc Cys	aag Lys	atc Ile	tcc Ser	agc Ser	cct Pro	tgc Cys	ttg Leu	aaa Lys	1968 .

					645					650		•			655		
5	gca Ala	gac Asp	agt Ser	gga Gly 660	gcc Ala	tgt Cys	ggt Gly	cca Pro	gac Asp 665	agc Ser	tgc Cys	ccc Pro	tac Tyr	tgt Cys 670	gcc Ala	cgg Arg	201.6
10	gcc Ala	ggg Gly	gca Ala 675	ggg Gly	gag Glu	gtg Val	gag Glu	ctc Leu 680	gcc Ala	gac Asp	cgt Arg	gaa Glu	atg Met 685	cct Pro	gac Asp	tca Ser	2064
10	gac Asp	agc Ser 690	gag Glu	gca Ala	gtt Val	tat Tyr	gag Glu 695	ttc Phe	aca Thr	cag Gln	gat Asp	gcc Ala 700	cag Gln	cac His	agc Ser	-	2112
15	ctc Leu 705	cgg Arg	gac Asp	ccc Pro	cac His	agc Ser 710	cgg Arg	cgg Arg	caa Gln	cgg Arg	agc Ser 715	ctg Leu	ggc Gly	cca Pro	gat Asp	gca Ala 720	2160
20	gag Glu	ccc Pro	agc Ser	tct Ser	gtg Val 725	ctg Leu	gcc Ala	ttc Phe	tgg Trp	agg Arg 730	cta Leu	atc Ile	tgt Cys	gac Asp	acc Thr 735	ttc Phe	2208
25	cga Arg	aag Lys	att Ile	gtg Val 740	gac Asp	agc Ser	aag Lys	tac Tyr	ttt Phe 745	ggc Gly	cgg Arg	gga Gly	atc Ile	atg Met 750	atc Ile	gcc Ala	2256
30	atc Ile	ctg Leu	gtc Val 755	aac Asn	aca Thr	ctc Leu	agc Ser	atg Met 760	ggc Gly	atc Ile	gaa Glu	tac Tyr	cac His 765	gag Glu	cag Gln	ccc Pro	2304
30	gag Glu	gag Glu 770	ctt Leu	acc Thr	aac Asn	gcc Ala	cta Leu 775	gaa Glu	atc Ile	agc Ser	aac Asn	atc Ile 780	gtc Val	ttc Phe	acc Thr	agc Ser	2352
35	ctc Leu 785	ttt Phe	gcc Ala	ctg Leu	gag Glu	atg Met 790	ctg Leu	ctg Leu	aag Lys	ctg Leu	ctt Leu 795	gtg Val	tat Tyr	ggt Gly	ccc Pro	ttt Phe 800	2400
40	ggc Gly	tac Tyr	atc Ile	aag Lys	aat Asn 805	ccc Pro	tac Tyr	aac Asn	atc Ile	ttc Phe 810	gat Asp	ggt Gly	gtc Val	att Ile	gtg Val 815	gtc Val	2448
45	atc Ile	agc Ser	gtg Val	tgg Trp 820	gag Glu	atc Ile	gtg Val	ggc Gly	cag Gln 825	cag Gln	ggg ggg	ggc Gly	ggc Gly	ctg Leu 830	tcg Ser	gtg Val	2496
50	ctg Leu	cgg Arg	acc Thr 835	ttc Phe	cgc Arg	ctg Leu	atg Met	cgt Arg 840	gtg Val	ctg Leu	aag Lys	ctg Leu	gtg Val 845	cgc Arg	ttc Phe	ctg · Leu	2544
	ccg Pro	gcg Ala 850	ctg Leu	cag Gln	cgg Arg	cag Gln	ctg Leu 855	gtg Val	gtg Val	ctc Leu	atg Met	aag Lys 860	acc Thr	atg Met	gac Asp	aac Asn	2592
55	gtg Val 865	gcc Ala	acc Thr	ttc Phe	tgc Cys	atg Met 870	ctg Leu	ctt Leu	atg Met	ctc Leu	ttc Phe 875	atc Ile	ttc Phe	atc Ile	ttc Phe	agc Ser 880	2640
60	atc Ile	ctg Leu	ggc Gly	atg Met	cat His 885	ctc Leu	ttc Phe	ggc Gly	tgc Cys	aag Lys 890	ttt Phe	gcc Ala	tct Ser	gag Glu	cgg Arg 895	gat Asp	2688
	ggg Gly	gac Asp	acc	ctg Leu	cca Pro	gac Asp	cgg Arg	aag Lys	aat Asn	ttt Phe	gac Asp	tcc Ser	ttg Leu	ctc Leu	tgg Trp	gcc Ala	2736

				900					905					910			
5	atc Ile	gtc Val	act Thr 915	gtc Val	ttt Phe	cag Gln	atc Ile	ctg Leu 920	acc Thr	cag Gln	gag Glu	gac Asp	tgg Trp 925	aac Asn	aaa Lys	gtc Val	2784
10	ctc Leu	tac Tyr 930	aat Asn	ggt Gly	atg Met	gcc Ala	tcc Ser 935	acg Thr	tcg Ser	tcc Ser	tgg Trp	gcg Ala 940	gcc Ala	ctt Leu	tat Tyr	ttc Phe	2832
70	att Ile 945	gcc Ala	ctc Leu	atg Met	acc Thr	ttc Phe 950	ggc Gly	aac Asn	tac Tyr	gtg Val	ctc Leu 955	ttc Phe	aat Asn	ttg Leu	ctg Leu	gtc Val 960	2880
15	gcc Ala	att Ile	ctg Leu	gtg Val	gag Glu 965	ggc Gly	ttc Phe	cag Gln	gcg Ala	gag Glu 970	gga Gly	gat Asp	gcc Ala	aac Asn	aag Lys 975	tcc Ser	2928
20	gaa Glu	tca Ser	gag Glu	ccc Pro 980	gat Asp	ttc Phe	ttc Phe	tca Ser	ccc Pro 985	agc Ser	ctg Leu	gat Asp	ggt Gly	gat Asp 990	Gly. ggg	gac Asp	2 <sup>.</sup> 976
25	agg Arg	aag Lys	aag Lys 995	tgc Cys	ttg Leu	gcc Ala	Leu	gtg Val 1000	tcc Ser	ctg Leu	gga Gly	Glu	cac His 1005	ccg Pro	gaç Glu	ctg Leu	3024
30	Arg	aag Lys 1010	agc Ser	ctg Leu	ctg Leu	Pro	cct Pro 1015	ctc Leu	atc Ile	atc Ile	His	acg Thr 1020	gcc Ala	gcc Ala	aca Thr	ccc Pro	3072
	atg Met 1025	Ser	ctg Leu	ccc Pro	Lys	agc Ser 1030	acc Thr	agc Ser	acg Thr	Gly	ctg Leu 1035	ggc Gly	gag Glu	gcg Ala	ctg Leu	ggc Gly L040	3120
35	cct Pro	gcg Ala	tcg Ser	Arg	cgc Arg 1045	Thr	agc Ser	agc Ser	Ser	ggg Gly 1050	tcg Ser	gca Ala	gag Glu	Pro	ggg Gly 1055	gcg Ala	3168
40	gcc Ala	cac His	Glu	atg Met 1060	aag Lys	tca Ser	ccg Pro	Pro	agc Ser 1065	gcc Ala	cgc Arg	agc Ser	Ser	ccg Pro	cac His	agc Ser	3216
45	Pro	Trp	agc Ser 1075	Ala	Ala	Ser	agc Ser 1	$\mathtt{Trp}$	acc Thr	agc Ser	agg Arg	Arg	tcc Ser .085	agc Ser	cgg Arg	aac Asn	3264
50	Ser	ctc Leu .090	ggc Gly	cgt Arġ	gca Ala	Pro-	agc Ser .095	ctg Leu	aag Lys	cgg Arg	Arg	agc Ser 100	cca Pro	agt Ser	gga Gly	gag Glu	3312
	cgg Arg 1105	Arg	tcc Ser	ctg Leu	Leu	tcg Ser 110	gga Gly	gaa Glu	ggc Gly	Gln	gag Glu 115	agc Ser	cag Gln	gat Asp	gaa Glu 1	gag Glu 120	3360
<i>55</i> .	gag Glu	agc Ser	tca Ser	Glu	gag Glu 125	gag Glu	cgg Arg	gcc Ala	Ser	cct Pro 130	gcg Ala	ggc Gly	agt Ser	Asp	cat His	cgc Arg	3408
60	cac His	agg Arg	Gly	tcc Ser 140	ctg Leu	gag Glu	cgg Arg	Glu	gcc Ala 145	aag Lys	agt Ser	tcc Ser	Phe	gac Asp 150	ctg Leu	cca Pro	3456
	gac Asp	aca Thr	ctg Leu	cag Gln	gtg Val	cca Pro	Gly ggg	ctg Leu	cat His	cgc Arg	act Thr	gcc Ala	agt Ser	ggc Gly	cga Arg	ggg	3504

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			1155					1160					1165				
5	tct Ser 1	gct Ala 170	tct Ser	gag Glu	cac. His	Gln	gac Asp 1175	tgc Cys	aat Asn	ggc Gly	Lys	tcg Ser 1180	gct Ala	tca Ser	Gly	cgc Arg	3552
. 10	ctg Leu 1185	Ala	cgg Arg	gcc Ala	Leu	cgg Arg 1190	cct Pro	gat Asp	gac Asp	Pro	cca Pro 1195	ctg Leu	gat Asp	ggg Gly	Asp	gac Asp 1200	3600
	gcc Ala	gat Asp	gac Asp	Glu	ggc Gly 1205	aac Asn	ctg Leu	agc Ser	Lys	ggg Gly 1210	gaa Glu	cgg Arg	gtc Val	Arg	gcg Ala 1215	tgg Trp	3648
15	atc Ile	cga Arg	Ala	cga Arg 1220	ctc Leu	cct Pro	gcc Ala	Cys	tgc Cys 1225	ctc Leu	gag Glu	cga Arg	Asp	tcc Ser 1230	tgg Trp	tca Ser	3696
20	gcc Ala	Tyr	atc Ile 1235	ttc Phe	cct Pro	cct Pro	Gln	tcc Ser 1240	agg Arg	ttc Phe	cgc Arg	Leu	ctg Leu 1245	tgt Cys	cac His	cgg Arg	3744
25	atc Ile 1	atc Ile 250	acc Thr	cac His	aag Lys	Met	ttc Phe 1255	gac Asp	cac His	gtg Val	Val	ctt Leu 1260	gtc Val	atc Ile	atc Ile	tto Phe	3792
30	ctt Leu 1265	Asn	tgc Cys	atc Ile	Thr	atc Ile 1270	gcc Ala	atg Met	gag Glu	Arg	ccc Pro 1275	aaa Lys	att Ile	gac Asp	Pro	cac His 1280	3840
	agc Ser	gct Ala	gaa Glu	Arg	atc Ile 1285	ttc Phe	ctg Leu	acc Thr	Leu	tcc Ser 1290	aat Asn	tac Tyr	atc Ile	Phe	acc Thr 1295	gca Ala	3888
35	gtc Val	ttt Phe	Leu	gct Ala 300	gaa. Glu	atg Met	aca Thr	Val	aag Lys 1305	gtg Val	gtg Val	gca Ala	Leu	ggc Gly 1310	tgg Trp	tgc Cys	3936
40	ttc (	Gly	gag Glu. 315	cag Gln	gcg Ala	tac Tyr	Leu	cgg Arg 1320	agc Ser	agt Ser	tgg Trp	Asn	gtg Val .325	ctg Leu	gac Asp	ggg Gly	3984
45	ctg Leu 1	ttg Leu 330	gtg Val	ctc Leu	atc Ile	Ser	gtc Val 1335	atc Ile	gac Asp	att Ile	Leu	gtg Val 1340	tcc Ser	atg Met	gtc Val	tct Ser	4032
50	gac Asp 1345	agc Ser	ggc Gly	acc Thr	Lys	atc Ile .350	ctg Leu	ggc Gly	atg Met	Leu	agg Arg .355	gtg Val	ctg. Leu	cgg Arg	Leu	ctg Leu 360	4080
	cgg a Arg '	acc Thr	ctg Leu	Arg	ccg Pro .365	ctc Leu	agg Arg	gtg Val	Ile	agc Ser .370	cgg Arg	gcg Ala	cag Gln	Gly	ctg Leu 1375	aag Lys	4128
<i>55</i>	ctg ( Leu '	gtg Val	Val	gag Glu 380	acg Thr	ctg Leu	atg Met	Ser	tca Ser .385	ctg Leu	aaa Lys	ccc Pro	Ile	ggc Gly 390	aac Asn	att Ile	4176
60	gta ( Val	Val	atc Ile 395	tgc Cys	tgt Cys	gcc Ala	Phe	ttc Phe 400	atc Ile	att Ile	ttc Phe	Gly	atc Ile 405	ttg Leu	ggg Gly	gtg Val	4224
	cag d Gln 1	ctc Leu	ttc Phe	aaa Lys	ggg Gly	aag Lys	ttt Phe	ttc Phe	gtg. Val	tgc Cys	cag Gln	ggc Gly,	gag Glu	gat Asp	acc Thr	agg Arg	4272

	1410		1415		:	1420		
5	aac atc a Asn Ile T 1425	acc aat aaa hr Asn Lys	tcg gac Ser Asp 1430	tgt gcc Cys Ala	gag gcc Glu Ala 1435	agt tac Ser Tyr	Arg Trp '	gtc 4320 Val 440
10	cgg cac a Arg His L	ag tac aac ys Tyr Asn 1445	ttt gac Phe Asp	Asn Leu	ggc cag Gly Gln 1450	gcc ctg Ala Leu	atg tcc o Met Ser 1 1455	ctg 4368 Leu
	ttc gtt t Phe Val L	tg gcc tcc eu Ala Ser 1460	aag gat Lys Asp	ggt tgg Gly Trp 1465	gtg gac Val Asp	Ile Met	tac gat o Tyr Asp ( 470	ggg 4416 Sly
15	Leu Asp A	ct gtg ggc la Val Gly 75	Val Asp	cag cag Gln Gln 1480	ccc atc Pro Ile	atg aac Met Asn 1485	cac aac d His Asn I	ecc 4464 Pro .
20	tgg atg c Trp Met L 1490	tg ctg tac eu Leu Tyr	ttc atc Phe Ile 1495	tcg ttc Ser Phe	Leu Leu	att gtg Ile Val 1500	gcc ttc t Ala Phe I	ctt 4512 Phe
25	gtc ctg a Val Leu A 1505	ac atg ttt sn Met Phe ]	gtg ggt Val Gly 1510	gtg gtg Val Val	gtg gag Val Glu 1515	aac ttc Asn Phe	His Lys (	gt 4560 Cys 520
<i>30</i>	cgg cag c Arg Gln H	ac cag gag is Gln Glu 1525	gaa gag Glu Glu	Glu Ala	cgg cgg Arg Arg 1530	cgg gag Arg Glu	gag aag d Glu Lys A 1535	ege 4608 Arg
	cta cga a Leu Arg A	ga ctg gag rg Leu Glu 1540	aaa aag Lys Lys	aga agg Arg Arg 1545	aat cta Asn Leu	Met Leu	gac gat o Asp Asp V 550	jta 4656 /al
35	att gct t Ile Ala S 15	cc ggc agc er Gly Ser 55	Ser Ala	agc gct Ser Ala 1560	gcg tca Ala Ser	gaa gcc Glu Ala 1565	cag tgc a Gln Cys I	aaa 4704 Lys
40	cct tac to Pro Tyr T 1570	ac tcc gac yr Ser Asp	tac tcc Tyr Ser 1575	cgc ttc Arg Phe	Arg Leu	ctc gtc Leu Val .580	cac cac t His His I	tg 4752 eu
45	tgc acc a Cys Thr S 1585	gc cac tac er His Tyr l	Leu Asp	ctc ttc Leu Phe	atc aca Ile Thr 1595	Gly Val	Ile Gly L	tg 4800 eu 500
50	aac gtg g Asn Val V	tc acc atg al Thr Met 1605	gcc atg Ala Met	Glu His	tac cag Tyr Gln 1610	cag ccc Gln Pro	cag att c Gln Ile L 1615	etg 4848 Leu
	gat gag g Asp Glu A	ct ctg aag la Leu Lys 1620	atc tgc Ile Cys	aac tac Asn Tyr 1625	atc ttc Ile Phe	Thr Val	atc ttt g Ile Phe V 630	tc 4896 al
<i>55</i>	ttg gag to Leu Glu So 16	ca gtt ttc er Val Phe 35	Lys Leu	gtg gcc Val Ala .640	ttt ggt Phe Gly	ttc cgt Phe Arg 7	cgg ttc t Arg Phe P	tc 4944 Phe
60	cag gac ac Gln Asp A: 1650	gg tgg aac rg Trp Asn	cag ctg Gln Leu 1655	gac ctg Asp Leu	Ala Ile	gtg ctg ( Val Leu : .660	ctg tcc a Leu Ser I	tc 4992 le
	atg ggc a Met Gly I	tc acg ctg le Thr Leu.	gag gaa Glu Glu	atc gag Ile Glu	gtc aac Val Asn	gcc tcg ( Ala Ser 1	ctg ccc a Leu Pro I	tc 5040 le

	1665		1670	1675	5	1680
5	aac ccc a Asn Pro	acc atc atc Thr Ile Ile 1685	cgc atc at Arg Ile Me	ig agg gtg ctg et Arg Val Leu 1690	g ege att gee eg Arg Ile Ala Ar 169	g Val
10	ctg aag o Leu Lys 1	ctg ctg aag Leu Leu Lys 1700	atg gct gt Met Ala Va	ig ggc atg cgg al Gly Met Arg 1705	g gcg ctg ctg ga g Ala Leu Leu As 1710	c acg 5136 p Thr
	Val Met (	cag gcc ctg Gln Ala Leu 715	ccc cag gt Pro Gln Va 172	ıl Gly Asn Leu	gga ctt ctc tt Gly Leu Leu Ph 1725	c atg 5184 e Met
15	ttg ttg t Leu Leu I 1730	ttt ttc atc Phe Phe Ile	ttt gca gc Phe Ala Al 1735	a Leu Gly Val.	gag ctc ttt gg Glu Leu Phe Gl 1740	a gac 5232 y Asp
20	ctg gag t Leu Glu ( 1745	Cys Asp Glu	aca cac co Thr His Pr 750	c tgt gag ggc o Cys Glu Gly 1755	ctg ggc cgt ca Leu Gly Arg Hi	t gcc 5280 s Ala 1760
25	acc ttt c Thr Phe A	egg aac ttt Arg Asn Phe 1765	ggc atg gc Gly Met Al	c ttc cta acc a Phe Leu Thr 1770	ctc ttc cga gtc Leu Phe Arg Val 1779	l Ser
30	aca ggt g Thr Gly A	gac aat tgg Asp Asn Trp 1780	aat ggc at Asn Gly Il	t atg aag gac e Met Lys Asp 1785	acc ctc cgg gad Thr Leu Arg Asp 1790	tgt 5376 Cys
	Asp Gln G	gag tcc acc Slu Ser Thr 195	tgc tac aa Cys Tyr As 180	n Thr Val Ile	tcg cct atc tac Ser Pro Ile Tyn 1805	c ttt .5424 c Phe .
35	gtg tcc t Val Ser F 1810	tc gtg ctg Phe Val Leu	acg gcc ca Thr Ala Gl 1815	n Phe Val Leu	gtc aac gtg gtg Val Asn Val Val 1820	g atc 5472 . Ile
40	gcc gtg c Ala Val L 1825	eu Met Lys	cac ctg ga His Leu Gl: 830	g gag agc aac u Glu Ser Asn 1835	aag gag gcc aag Lys Glu Ala Lys	g gag 5520 s Glu 1840
45	gag gcc g Glu Ala G	ag cta gag lu Leu Glu 1845	Ala Glu Le	g gag ctg gag u Glu Leu Glu 1850	atg aag acc cto Met Lys Thr Lev 1855	Ser
50	ccc cag c Pro Gln P	cc cac tcg ro His Ser 1860	cca ctg gg Pro Leu Gl	c agc ccc ttc y Ser Pro Phe 1865	ctc tgg cct ggg Leu Trp Pro Gly 1870	gtc 5616 Val
	GIU GIY P	cc gac agc ro Asp Ser 75	ccc gac ago Pro Asp Se: 1880	r Pro Lys Pro	ggg gct ctg cac Gly Ala Leu His 1885	cca. 5664 Pro
<i>55</i>	gcg gcc c Ala Ala H 1890	ac gcg aga is Ala Arg	tca gcc tco Ser Ala Sei 1895	r His Phe Ser	ctg gag cac ccc Leu Glu His Pro 1900	acg 5712 Thr
60	atg cag c Met Gln P 1905	ro His Pro	acg gag cto Thr Glu Leo 910	g cca gga cca ı Pro.Gly Pro 1915	gac tta ctg act Asp Leu Leu Thr	gtg 5760 Val 1920
	cgg aag t Arg Lys S	ct ggg gtc er Gly Val	agc cga acc Ser Arg Thi	g cac tot otg	ccc aat gac agc Pro Asn Asp Ser	tac ·5808 Tyr

		1925	1930	1935	
5	Met Cys Arg	cat ggg agc act His Gly Ser Thr 940	gcc gag ggg ccc Ala Glu Gly Pro 1945	ctg gga cac agg ggc Leu Gly His Arg Gly 1950	5856
10	tgg ggg ctc ( Trp Gly Leu : 1955	cec aaa get cag Pro Lys Ala Gin	tca ggc tcc gtc Ser Gly Ser Val 1960	ttg tcc gtt cac tcc Leu Ser Val His Ser 1965	5904
10	cag cca gca o Gln Pro Ala i 1970	gat acc agc tac Asp Thr Ser Tyr 1975	Ile Leu Gln Leu	ccc aaa gat gca cct Pro Lys Asp Ala Pro 1980	5952
15	cat ctg ctc o His Leu Leu ( 1985	cag ccc cac ago Gln Pro His Ser 1990	gcc cca acc tgg Ala Pro Thr Trp 1995	ggc acc atc ccc aaa Gly Thr Ile Pro Lys 2000	600 <u>0</u>
20	ctg ccc cca c Leu Pro Pro I	cca gga cgc tcc Pro Gly Arg Ser 2005	cct ttg gct cag Pro Leu Ala Gln 2010	agg cca ctc agg cgc Arg Pro Leu Arg Arg 2015	6048
25	GIN Ala Ala	ata agg act gac Ile Arg Thr Asp J20	tcc ttg gac gtt Ser Leu Asp Val 2025	cag ggt ctg ggc agc Gln Gly Leu Gly Ser 2030	6096
30	cgg gaa gac d Arg Glu Asp I 2035	Leu Leu Ala Glu	gtg agt ggg ccc Val Ser Gly Pro 2040	tcc ccg ccc ctg gcc Ser Pro Pro Leu Ala 2045	6144
	cgg gcc tac t Arg Ala Tyr S 2050	ect ttc tgg ggc Ser Phe Trp Gly 2055	Gln Ser Ser Thr	cag gca cag cag cac Gln Ala Gln Gln His 060	6192
35	tcc cgc agc o Ser Arg Ser H 2065	cac agc aag atc lis Ser Lys Ile 2070	tcc aag cac atg Ser Lys His Met 2075	acc ccg cca gcc cct Thr Pro Pro Ala Pro 2080	6240
40	tgc cca ggc c Cys Pro Gly F	cca gaa ccc aac Pro Glu Pro Asn 2085	tgg ggc aag ggc Trp Gly Lys Gly 2090	cct cca gag acc aga Pro Pro Glu Thr Arg 2095	6288
45	Ser Ser Leu G	gag ttg gac acg Glu Leu Asp Thr .00	gag ctg agc tgg Glu Leu Ser Trp 2105	att tca gga gac ctc Ile Ser Gly Asp Leu 2110	6336
50	ctg ccc cct g Leu Pro Pro G 2115	Sly Gly Gln Glu	gag ccc cca tcc Glu Pro Pro Ser 2120	cca cgg gac ctg aag Pro Arg Asp Leu Lys 2125	6384
	aag tgc tac a Lys Cys Tyr S 2130	gc gtg gag gcc Ser Val Glu Ala 2135	Gln Ser Cys Gln .	cgc cgg cct acg tcc Arg Arg Pro Thr Ser 140	6432
<b>55</b>	tgg ctg gat g Trp Leu Asp G 2145	ag cag agg aga Blu Gln Arg Arg 2150	cac tct atc gcc His Ser Ile Ala 2155	gtc agc tgc ctg gac Val Ser Cys Leu Asp 2160	6480
60	agc ggc tcc c Ser Gly Ser G	aa ccc cac ctg In Pro His Leu 2165	ggc aca gac ccc : Gly Thr Asp Pro : 2170	tct aac ctt ggg ggc Ser Asn Leu Gly Gly 2175	6528
	cag cct ctt g Gln Pro Leu G	gg ggg cct ggg ly Gly Pro Gly	agc cgg ccc aag s Ser Arg Pro Lys	aaa aaa ctc agc ccg Lys Lys Leu Ser Pro	6576

	218	9	2135	2190	
5	cct agt atc ac Pro Ser Ile Th 2195	c ata gas coor	c ccc gag ago o Pro Glu Ser 2200 .	caa ggt oot ogg Gin Gly Pro Arg 2205	acc ccg 6624 Thr Pro
10	ccc agc cct gg Pro Ser Pro Gl 2210	t ato tgo oto y Ile Cys Leu 2215	u Arg Arg Arg	gót ceg tee age Ala Pro Ser Ser 2220	gac too 6672 Asp Ser
10	aag gat ccc tt Lys Asp Pro Le 2225	g god tot ggd u Ala Ser Gly 2230	c ccc cct gac y Pro Pro Asp	ago atg got goo Ser Met Ala Ala 2235	tog coc 6720 Ser Pro 2240
15	tcc cca aag aa Ser Pro Lys Ly	a gat gtg ctg s Asp Val Leu 2245	g agt ctc tcc 1 Ser Lau Ser 2250	ggt tta too tot Gly Leu Ser Ser	gac cca 6769 Asp Pro 2255
20	gca gac ctg ga Ala Asp Leu As 226	p Pro			6783
25	<210> 3 <211> 6804 <212> DNA <213> Homo sap	iens			
30	<220> <221> CDS <222> (1)(68	04)			
35	<400> 3 atg gac gag ga Met Asp Glu Glo 1	g gag gat gga u Glu Asp Gly 5	geg gge gee Ala Gly Ala 10	gag gag tcg gga Glu Glu Ser Gly	cag ccc 48 Gln Pro 15
40	cgg agc ttc atc Arg Ser Phe Mer 20	t Arg Leu Asn	gac ctg tcg Asp Leu Ser 25	ggg gcc ggg ggg Gly Ala Gly Gly 30	cgg ccg 96 . Arg Pro
45	ggg ccg ggg tca Gly Pro Gly Sea 35	a gca gaa aag r Ala Glu Lys	gac ccg ggc Asp Pro Gly 40	agc gcg gac tcc Ser Ala Asp Ser 45	gag gcg 144 Glu Ala
	gag ggg ctg ccc Glu Gly Leu Pro 50	g tac ccg gcg o Tyr Pro Ala 55	Leu Ala Pro	gtg gtt ttc ttc Val Val Phe Phe 60	tac ttg 192 Tyr Leu
50	agc cag gac agc Ser Gln Asp Ser 65	c cgc ccg cgg c Arg Pro Arg 70	age tgg tgt Ser Trp Cys	ctc cgc acg gtc Leu Arg Thr Val 75	tgt aac 240 Cys Asn 80
<i>55</i>	eccitgg ttt gag Pro Trp Phe Glu	g cgc atc agc 1 Arg Ile Ser 85	atg ttg gtc Met Leu Val 90	atc ctt ctc aac Ile Leu Leu Asn	tgc gtg 288 Cys Val 95
60	acc ctg ggc ato Thr Leu Gly Met 100	: Phe Arg Pro	tgc gag gac Cys Glu Asp 105	atc gcc tgt gac Ile Ala Cys Asp 110	tcc cag 336 Ser Gln
	cgc tgc cgg ato Arg Cys Arg Ile 115	c ctg cag gcc E Leu Gln Ala	ttt gat gac Phe Asp Asp 120	tto ato ttt goo Phe lle Phe Ala 125	tto ttt 384 Phe Phe

5	gcc Ala	gtg Val 130	gag Glu	aig Met	gtg Val	gtg Val	aag Lys 135	atg Met	gtg Val	gcc Ala	tig Leu	ggc Gly 140	atc Ile	ttt Phe	Gly 333	aaa Lys	432
	aag Lys 145	tgt Cys	tac Tyr	ctg Leu	gga Gly	gac Asp 150	act Thr	<u>Lib</u> Edd	aac Asn	cgg Arg	ctt Leu 155	gac Asp	ttt Pne	tto Pne	atc Ile	gtc Val 160	480 -
10	atc Ile	gca Ala	ggg Gly	atg Met	ctg Leu 165	gag Glu	tac Tyr	tog Ser	ctg Leu	gac Asp 170	ctg Leu	cag Gln	aac Asn	gtc Val	agc Ser 175	ttc Phe	528
15	tca Ser	gct Ala	gtc Val	agg Arg 180	aca Thr	gtc Val	cgt Arg	gtg Val	ctg Leu 185	cga Arg	ccg Pro	ctc Leu	agg Arg	gcc Ala 190	att Ile	aac Asn	576.
20	cgg Arg	gtg Val	ccc Pro 195	agc Ser	atg Met	cgc Arg	atc Ile	ctt Leu 200	gtc Val	acg Thr	ttg Leu	ctg Leu	ctg Leu 205	gat Asp	acg Thr	ctg Leu	624
25	ccc Pro	atg Met 210	ctg Leu	ggc Gly	aac Asn	gtc Val	ctg Leu 215	ctg Leu	ctc Leu	tğc Cys	ttc Phe	ttc Phe 220	gtc Val	ttc Phe	ttc Phe	atc Ile	672
	ttc Phe 225	ggc Gly	atc Ile	gtc Val	ggc Gly	gtc Val 230	cag Gln	ctg Leu	tgg Trp	gca Ala	ggg Gly 235	ctg Leu	ctt Leu	cgg Arg	aac Asn	cga Arg 240	720
30															ctg Leu 255		768
35	cgc Arg	tat Tyr	tac Tyr	cag Gln 260	aca Thr	gag Glu	aac Asn	gag Glu	gat Asp 265	gag Glu	agc Ser	ccc Pro	ttc Phe	atc Ile 270	tgc Cys	tcc Ser	816
40															acg Thr		864
45															gag Glu		912
															tac Tyr		960
50															atc Ile 335		1008
<i>55</i>															atc Ile		1056
60							Ile								cat His		1104
	ttc Phe	tac Tyr 370	aat Asn	ttc Phe	atc Ile	tac Tyr	ttc Phe 375	atc Ile	ctc Leu	ctc Leu	atc Ile	atc Ile 380	gtg Val	ggc Gly	tcc Ser	ttc Phe	1152

5	ttc Phe 385	atg Met	atc Ile	aac Asn	ctg Leu	tgc Cys 390	ctg Leu	gig Val	gtg Val	att	gcc Ala 395	acg Thr	cag Gln	tto Phe	tca Ser	gag Glu 400	1200
J	acc Thr	aag Lys	cag Gln	cgg Arg	gaa Glu 405	agc Ser	cag Gln	otg Leu	atg Met	cgg Arg 410	gag Glu	cag Gln	egt Arg	gig Val	cgg Arg 415	ttc Phe	1248
10	ctg Leu	tcc Ser	aac Asn	gcc Ala 420	agc Ser	acc Thr	ctg Leu	gct Ala	agc Ser 425	ttc Phe	tct Ser	gag Glu	ccc Pro	ggc Gly 430	agc Ser	tgc Cys	1296
15	tat Tyr	gag Glu	gag Glu 435	ctg Leu	ctc Leu	aag Lys	tac Tyr	ctg Leu 440	gtg Val	tac Tyr	atc Ile	ctt Leu	cgt Arg 445	aag Lys	gca Ala	gcc Ala	1344
20	cgc Arg	agg Arg 450	ctg Leu	gct Ala	cag Gln	gtc Val	tct Ser 455	cgg Arg	gca Ala	gca Ala	ggt Gly	gtg Val 460	cgg Arg	gtt Val	ggg Gly	ctg Leu	1392
25	ctc Leu 465	agc Ser	agc Ser	cca Pro	gca Ala	ccc Pro 470	ctc Leu	GJ À âàà	ggc Gly	cag Gln	gag Glu 475	acc Thr	cag Gln	ccc Pro	agc Ser	agc Ser 480	1440
23	agc Ser	tgc Cys	tct Ser	cgc Arg	tcc Ser 485	cac His	cgc Arg	cgc Arg	cta Leu	tcc Ser 490	gtc Val	cac His	cac His	ctg Leu	gtg Val 495	cac His	1488
30	cac His	cac His	cac His	cac His 500	cat His	cac His	cac His	cac His	tac Tyr 505	cac His	ctg Leu	ggc Gly	aat Asn	ggg Gly 510	acg Thr	ctc Leu	1536
35	agg Arg	gcc Ala	ccc Pro 515	cgg Arg	gcc Ala	agc Ser	ccg Pro	gag Glu 520	atc Ile	cag Gln	gac Asp	agg Arg	gat Asp 525	gcc Ala	aat Asn	ggg Gly	1584
40	tcc Ser	cgc Arg 530	cgg Arg	ctc Leu	atg Met	ctg Leu	cca Pro 535	cca Pro	ccc Pro	tcg Ser	acg Thr	cct Pro 540	gcc Ala	ctc Leu	tcc Ser	Gly ggg	1632
.45	gcc Ala 545	ccc Pro	cct Pro	ggt Gly	ggc Gly	gca Ala 550	gag Glu	tct Ser	gtg Val	cac His	agc Ser 555	ttc Phe	tac Tyr	cat His	gcc Ala	gac Asp 560	1680
. 43	tgc Cys	cac His	tta Leu	gag Glu	cca Pro 565	gtc Val	cgc Arg	tgc Cys	cag Gln	gcg Ala 570	ccc Pro	cct Pro	ccc Pro	agg Arg	tcc Ser 575	cca Pro	1728
50	tct Ser	gag Glu	gca Ala	tcc Ser 580	ggc Gly	agg Arg	act Thr	gtg Val	ggc Gly 585	agc Ser	ggg Gly	aag Lys	gtg Val	tat Tyr 590	Pro	acc Thr	1776
55	gtġ Val	cac His	acc Thr 595	agc Ser	cct Pro	cca Pro	Pro ccg	gag Glu 600	acg Thr	ctg Leu	aag Lys	gag Glu	aag Lys 605	gca Ala	cta Leu	gta Val	1824
60	gag Glu	gtg Val 610	Ala	gcc Ala	agc Ser	tct Ser	gag Gly 615	Pro	cca Pro	acc Thr	ctc Leu	acc Thr 620	agc Se≍	ctc Leu	aac Asn	atc Ile	1872
	cca Pro 625	Pro	Gly	ccc Pro	tac Tyr	agc Ser 630	Ser	atg Met	cac	aag Lys	ctg Leu 635	Leu	gag Glu	aca Thr	cag Gln	agt Ser 640	1920

5	aca Thr	Gly	gcc Ala	tgc Cys	caa Gln 645	agc Ser	to: Ser	tgc Cys	aag Lys	atc Ile 650	Ser	agc Ser	Pro	tgo Cys	tog Leu 655	aaa Lys	1963
	gca Ala	gac Asp	agt Ser	gga Gly 660	goo Ala	tgt Cys	ggt Gly	Pro	gac Asp 665	agc Ser	tgc Cys	ccc Pro	tac .Tyr	tgt Cys 670	goo Ala	ogg Arg	2016
10	gcc Ala	Gly	gca Ala 675	Gly	gag Glu	gtg Val	gag Glu	ctc Leu 680	gcc Ala	gac Asp	ogt Arg	gaa Glu	atg Met 685	cct Pro	gac Asp	tca Ser	2064
15	gac Asp	agc Ser 690	gag Glu	gca Ala	gtt Val	tat Tyr	gag Glu 695	ttc Phe	aca Thr	cag Gln	gat Asp	gcc Ala 700	cag Gln	cac His	ago Ser	gac Asp	2112
20	ctc Leu 705	cgg Arg	gac Asp	ccc Pro	cac His	agc Ser 710	cgg Arg	cgg Arg	caa Gln	cgg Arg	agc Ser 715	ctg Leu	ggc	cca Pro	gat Asp	gca Ala 720	2160
25	gag Glu	ccc Pro	agc Ser	tct Ser	gtg Val 725	Leu	gcc Ala	ttc Phe	tgg Trp	agg Arg 730	cta Leu	atc Ile	tgt. Cys	gac Asp	acc Thr 735	ttc Phe	2208
	cga Arg	aag Lys	att Ile	gtg Val 740	gac Asp	agc Ser	aag Lys	tac Tyr	ttt Phe 745	ggc Gly	cgg Arg	gga Gly	atc Ile	atg Met 750	atc Ile	gcc Ala	. 2256
30	atc Ile	ctg Leu	gtc Val 755	aac Asn	aca Thr	ctc Leu	agc Ser	atg Met 760	ggc Gly	atc Ile	gaa Glu	tac Tyr	cac His 765	gag Glu	cag Gln	ccc Pro	2304
35	gag Glu	gag Glu 770	ctt Leu	acc Thr	aac Asn	gcc Ala	cta Leu 775	gaa Glu	atc Ile	agc Ser	aac Asn	atc Ile 780	gtc Val	ttc Phe	acc Thr	agc Ser	2352
40	ctc Leu 785	ttt Phe	gcc Ala	ctg Leu	gag Glu	atg Met 790	ctg Leu	ctg Leu	aag Lys	ctg Leu	ctt Leu 795	gtg Val	tat Tyr	ggt Gly.	ccc. Pro	ttt Phe 800	2400
45	ggc Gly	tac Tyr	àtc Ile	aag Lys	aat Asn 805	ccc Pro	tac Tyr	aac Asn	atc Ile	ttc Phe 810	gat Asp	ggt Gly	gtc Val	att Ile	gtg Val 815	gtc Val	2448
	atc Ile	agc Ser	gtg Val	tgg Trp 820	gag Glu	atc Ile	gtg Val	ggc Gly	cag Gln 825	cag Gln	G] À aaa	ggc Gly	ggc Gly	ctg Leu 830	tcg Ser	gtg Val	. 2496
50	ctg Leu	cgg Arg	acc Thr 835	ttc Phe	cgc Arg	ctg Leu	atg Met	cgt Arg 840	gtg Val	ctg Leu	aag Lys	ctg Leu	gtg Val 845	cgc Arg	ttc Phe	ctg Leu	2544
<b>55</b>	ccg Pro	gcg Ala 850	ctg Leu	cag Gln	cgg Arg	cag Gln	ctg Leu 855	gtg Val	gtg Val	ctc Leu	atg Met	aag Lys 860	acc Thr	atg Met	gac Asp	aac Asn	. 2592
60	gtg Val 865	gcc Ala	acc Thr	ttc Phe	tgc Cys	atg Met 870	ctg Leu	ctt Leu	atg Met	ctc Leu	ttc Phe 875	atc Ile	ttc Phe	atc Ile	ttc Phe	agc Ser 380	2640
	atc Ile	ctg Leu	ggc Gly	atg Met	cat His 885	ctc Leu	ttc Phe	gge Gly	tgc Cys	aag Lys 390	ttt Phe	gcc Ala	tct Ser	gag Glu	832 Yza caa	gat Asp	2688

5	Gly	gac Asp	acc Thr	ctg Leu 900	cca Pro	ysb dec	Arg	aag Lys	aat Asn 905	ttt Phe	gac Asp	tcc Ser	ttg Leu	ctc Leu 910	tgg Trp	gcc Ala	2736
	atc Ile	gtc Val	act Thr 915	gtc Val	ttt Phe	cag Gln	atc Ile	ctg Leu 920	acc Thr	cag Gln	gag Glu	gac Asp	tgg Trp 925	aac Asn	aaa Lys	gto Val	2784
10	ctc Leu	tac Tyr 930	aat Asn	ggt Gly	atg Met	gcc Ala	Ser 935	acg Thr	tcg Ser	tcc Ser	tgg Trp	gcg Ala 940	gcc Ala	ctt Leu	tat Tyr	ttc Phe	2832
15	att Ile 945	gcc Ala	ctc Leu	atg Met	acc Thr	ttc Phe 950	ggc Gly	aac Asn	tac Tyr	gtg Val	ctc Leu 955	ttc Phe	aat Asn	ttg Leu	ctg Leu	gtc Val 960	2830
20	gcc Ala	att Ile	ctg Leu	gtg Val	gag Glu 965	ggc Gly	ttc Phe	cag Gln	gcg Ala	gag Glu 970	gga Gly	gat Asp	gcc Ala	aac Asn	aag Lys 975	tcc Ser	2928
25	gaa Glu	tca Ser	gag Glu	ccc Pro 980	gat Asp	ttc Pne	ttc Phe	tca Ser	ccc Pro 985	agc Ser	ctg Leu	gat Asp	ggt Gly	gat Asp 990	GļĀ āāā	gac Asp	2976
	agg Arg	aag Lys	aag Lys 995	tgc Cys	ttg Leu	gcc Ala	Leu	gtg Val .000	tcc Ser	ctg Leu	gga Gly	Glu	cac His 1005	ccg Pro	gag Glu	ctg Leu	3024
30	Arg					₽ro					His				aca Thr		3072
35	atg Met 1025	Ser	ctg Leu	ccc Pro	Lys	agc Ser 1030	acc Thr	agc Ser	acg Thr	Gly	ctg Leu .035	ggc Gly	gag Glu	gcg Ala	ctg Leu	ggc Gly .040	3120
40				Arg					Ser					Pro	ggg Gly. 1055		3168
<b>4</b> 5	gcc Ala	cac His	Glu	atg Met 1060	aag Lys	tca Ser	ccg Pro	Pro	agc Ser .065	gcc Ala	cgc Arg	agc Ser	Ser	ccg Pro .070	cac His	agc Ser	3216
	ccc Pro	Trp	agc Ser .075	gct Ala	gca Ala	agc Ser.	Ser	tgg Trp 080	acc Thr	agc Ser	agg Arg	Arg	tcc Ser .085	agc Ser	cgg Arg	aac Asn	3264
50	Ser	ctc Leu .090	ggc Gly	cgt Arg	gca Ala	Pro	agc Ser 095	ctg Leu	aag Lys	cgg Arg	Arg	agc Ser 100	cca Pro	agt Ser	gga Gly	gag Glu	3312
<i>55</i>		Arg			Leu					Gln					gaa Glu 1		3360
60	gag Glu	agc Ser	tca Ser	Glu	gag. Glu 125	gag Glu	egg Arg.	gcc Ala	Ser	cct Pro 130	gcg Ala	ggc ' Gly	agt Ser	Asp	cat His 135	cgc Arg	3405
	cac His	agg Arg	Gly	tcc Ser 140	ctş Leu	gag. Glu	agg Arg	Glu.	gcc Ala 145	aag Lys	agt Ser	tcc Ser	Phe	gac Asp 150	ctg Leu	cca Pro	3456

<u> 5</u>		Thr					Gly					Ala	agt Ser 1165				3504
	Ser					Gln					Lys		gct Ala				3552
10		Ala			Leu					Pro			gat Asp		Asp		3600
15				Glu					Lys				gtc Val	Arg			3648
20			Ala					Cys					gac Asp				3696
25		Tyr					Gln					Leu	ctg Leu L245			cgg . Arg	3744
	Ile					Met					Val		gtc Val				3792
30		Asn			Thr					Arg			att Ile		Pro		3840
35				Arg					Leu				atc Ile	Phe			3888.
40			Leu					Val					ctg Leu 1				3936
45		Gly					Leu					Asn	gtg Val 1325				3984
	Leu					Ser					Leu		tcc Ser				4032
50		Ser			Lys					Leu			ctg Leu		Leu		4080
<i>55</i>				Arg					Ile				cag Gln	Gly			4128
60			Val					Ser					atc <sup>.</sup> Ile				4176
		Val					Phe					Gly	atc Ile 1405				4224

5	cag ct: Gln Let 1413	: Phe	: aaa : Lys	G1 y	aag Lys	ttt Phe 1415	tt: Phe	gtg Val	tgo Cys	cag Gln	ggo Gly 1420	Glu	gat Asp	acc Thr	agg.	<del>1</del> 272
	aac atc Asn Ile 1425	acc Thr	aat Asn	Lys	tcg Ser 1430	gac Asp	tgt Cys	gcc Ala	Glu	gcc Ala 1435	Ser	tac Tyr	cgg Arg	tgg Trp	gtc Val 1440	÷320
10	ogg dad Arg His	: aag : Lys	Tyr	aac Asn 1445	ttt Phe	gac Asp	aac Asn	Leu	ggc Gly 1450	cag Gln	gcc Ala	ctg Leu	Met	tcc Ser 1455	Leu	÷363
15	tto git Phe Val	Leu	gcc Ala 1460	tcc Ser	aag Lys	gat Asp	Gly	tgg Trp 1465	gtg ·Val	gac Asp	atc Ile	Met	tac Tyr 1470	gat Asp	Gly	4416
20	ctg gat Leu Asp	gct Ala 1475	gtg Val	ggc Gly	gtg Val	Asp	cag Gln 1480	cag Gln	ccc Pro	atc Ile	Met	aac Asn 1485	cac His	aac Asn	ccc Pro	4464
25	tgg atg Trp Met 1490	Leu	ctg Leu	tac Tyr	Phe	atc Ile 1495	tcg Ser	ttc Phe	ctg Leu	Leu	att Ile 1500	gtg Val	gcc Ala	ttc Phe	ttt Phe	4512
	gtc ctg Val Leu 1505	aac Asn	atg Met	Phe	gtg Val L510	ggt Gly	gtg Val	gtg Val	Val	gag Glu 1515	aac Asn	ttc Phe	cac His	Lys	tgt Cys 1520	4560
30	cgg cag Arg Cln	cac	Gln	gag Glu L525	gaa Glu	gag Glu	gag Glu	Ala	cgg Arg 1530	cgg Arg	cgg Arg	gag Glu	Glu	aag Lys 1535	cgc Arg	4608
35	cta cga Leu Arg	Arg	ctg Leu L540	gag Glu	aaa Lys	aag Lys	Arg	agg Arg 1545	agt Ser	aag Lys	gag Glu	Lys	cag Gln L550	atg Met	gct Ala	4656
40	gat cta Asp Leu	atg Met 1555	ctg Leu	gac Asp	gat Asp	Val	att Ile 560	gct Ala	tcc Ser	ggc Gly	Ser	tca Ser .565	gcc Ala	agc Ser	gct Ala	4704
45	gcg tca Ala Ser 1570	gaa Glu	gcc Ala	cag Gln	Cys	aaa Lys 575	cct Pro	tac Tyr	tac Tyr	Ser	gac Asp .580	tac Tyr	tcc Ser	cgc Arg	ttc Phe	<b>4</b> 752
,,,	cgg ctc Arg Leu 1585	ctc Leu	gtc Val	His	cac His 590	ttg Leu	tgc Cys	acc Thr	Ser	cac His 595	tac Tyr	ctg Leu	gac Asp	Leu	ttc Phe .600	4900
50	atc aca Ile Thr	ggt Gly	Val	atc Ile 605	Gly ggg	ctg Leu	aac Asn	Val	gtc Val 610	acc Thr	atg Met	gcc Ala	Met	gag Glu 615	cac His	4848
55	tac cag Tyr Gln	Gln	ccc Pro .620	cag Gln	att Ile	ctg Leu	Asp	gag Glu .625	Ala	ctg Leu	aag Lys	Ile	tgc Cys 630	aac Asn	tac Tyr	4896
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	ttt ggt Phe Gly 1650	ttc Phe	cgt Arg	cgg Arg	Phe	ttc Phe 653	cag Gln	gac Asp	agg Arg	Trp	aac Asn 660	cag Gln	ctg Leu	gac Asp	ctg Leu	4992

5	gcc att d Ala Ile V 1665				Gly Ile				5040
	gto aac o Val Asn A	Ala Ser	ctg ccc Leu Pro 1685	ato aac Ile Asn	ccc acc Pro Thr 1690	Ile Ile	ogo ato Arg Ile	atg agg Met Arg 1695	5088
10	gtg ctg o							Val Gly	5136
15	atg cgg ( Met Arg )				Met Gln	Ala Leu			5184
20	aac ctg o Asn Leu (		Leu Phe						5232
25	ggc gtg o Gly Val o 1745				Glu Cys				5280
	gag ggc o Glu Gly i	Leu Gly							. 5328
30	cta acc o			Ser Thr				Ile Met	5376
35	aag gac a Lys Asp 1				Gln Glu	Ser Thr			542,4,
40	gtc atc s Val Ile s 1810		Ile Tyr					cag ttc Gln Phe	5472
45	gtg cta o Val Leu v 1825				Val Leu				5520
	agc aac a Ser Asn 1	Lys Glu					Ala Glu		5568
50	ctg gag a Leu Glu I			Ser Pro					5616
55	Pro Phe				Gly Pro	Asp Ser		age ecc Ser Pro	5664
60	aag cct ( Lys Pro ( 1890		Leu His				Ser Ala	tcc cac Ser His	5712
	ttt tcc Phe Ser 1905	ctg gag Leu Glu	cac ccc His Pro 1910	acg atg Thr Met	Gìn Pro	cac ccc His Pro 1915	acg gag Thr Glu	ctg cca Leu Pro 1920	5760

<i>5</i>	gga cca Gly Pro	gac Asp	Leu	ctg Leu 925	act Thr	gtg Val	cgg Arg	Lys	tct Ser 1930	Gly , Gly	gto Val	ser	Arg	acç Thr 1935	cac His	5808
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40	agt acc Ser Thr 2065			Gln					Ser					Ser		6240
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	atc gcc Ile Ala		Ser (					Gly					Leu			6528

ĵ.	gac cc: Asp Pro	tot Ser	aac Asn 2180	ctt Leu	ggg	Gjà ggc	Gln	ect Pro 2185	ct c Leu	61% 848	G1y aga	Pro	999 Gly 2190	ser Ser	cgg Arg	6576
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40	cgg ago								10					1 9		
	Arg Ser	ttc Phe	atg Met 20	cgg Arg	ctc Leu	aac Asn	gac Asp	ctg Leu 25	tcq	Gly aga	gcc Ala	Gļā āāā	ggg Gly 30	caa	ccg Pro	96
45	Arg Ser ggg ccg Gly Pro	Phe	Met 20	Arg	Leu	Asn	Asp	Leu 25 ccq	tcg Ser	Gly	Ala	Gly	Gly 30	cgg Arg	Pro	96
45 50	Arg Ser	ggg Gly 35 ctg Leu	Met 20 tca Ser	Arg gca Ala tac	gaa Glu ccg	Asn aag Lys gcg	gac Asp 40	Leu 25 ccg Pro	tcg Ser ggc Gly	Gly agc Ser	Ala gcg Ala gtt	Gly gac Asp 45	Gly 30 tcc Ser	cgg Arg gag Glu	Pro gcg Ala	
	ggg ccg Gly Pro gag ggg Glu Gly	Phe ggg Gly 35 ctg Leu gac	Met 20 tca Ser ccg Pro	Arg gca Ala tac Tyr	gaa Glu ccg Pro	Asn aag Lys gcg Ala 55	gac Asp 40 ctg Leu	Leu 25 ccg Pro gcc Ala	tcg Ser ggc Gly ccg Pro	Gly agc Ser gtg Val	Ala gcg Ala gtt Val 60	Gly gac Asp 45 ttc Phe	Gly 30 tcc Ser ttc Phe	cgg Arg gag Glu tac Tyr	gcg Ala ttg Leu	144
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15	cag go Gln Al		Leu					Asn					Phe				5136
20	ttt tt Phe Pr	ne.	atc Ile 715	ttt Phe	gca Ala	gct Ala	Leu	ggc Gly 1720	gtg Val	gag Glu	ctc Leu	Phe	gga Gly 1725	gac Asp	ctg Leu	gag Glu	5184
	tgt ga Cys As 173	q2	gag Glu	aca Thr	cac His	Pro	tgt Cys .735	gag Glu	ggc Gly	ctg Leu	Gly	cgt Arg .740	cat His	gcc Ala	acc Thr	ttt Phe	5232
25	cgg aa Arg As 1745	ac sn	ttt Phe	gly	Met	gcc Ala 1750	ttc Phe	cta Leu	acc Thr	Leu	ttc Phe 1755	cga Arg	gtc Val	tcc Ser	Thr	ggt Gly L760	5280
30	gac aa Asp As	at sn	tgg Trp	Asn	ggc Gly L765	att Ile	atg Met	aag Lys	Asp	acc Thr 1770	ctc Leu	cgg Arg	gac Asp	Cys	gac Asp 1775	cag Gln	5328
35	gag to Glu Se		Thr					Val					Tyr				5376
40	ttc gt Phe Va	1	ctg Leu 795	acg Thr	gcc Ala	cag Gln	Phe	gtg Val .800	cta Leu	gtc Val	aac Asn	Val	gtg Val .805	atc Ile	gcc Ala	gtg Val	5424
	ctg at Leu Me 181	et :	aag Lys	cac His	ctg Leu	Glu	gag Glu .815	agc Ser	aac Asn	aag Lys	Glu	gcc Ala 820	aag Lys	gag Glu	gag Glu	gcc Ala	5472
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50	ccc ca Pro Hi			Pro					Phe					Val			5568
55	ccc ga Pro As	ic a	Ser	ccc Pro 860	gac Asp	agc Ser	ccc Pro	Lys	cct Pro .865	GJ À G À À	gct. Ala	ctg Leu	His	cca Pro 1870	Ala	gcc Ala	5616
60	cac go His Al	a					His					His					5664
	ccc ca Pro Hi 189	s:				Leu					Leu						5712

	tot ggg Ser Gly 1905			Arg					Pro					Met		5760
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10	ctc ccc Leu Pro	Lys					Ser					His				5856
15	gca gat Ala Asp					Leu					Asp					5904
20	ctc cag Leu Gin 1970	ccc Pro	cac His	agc Ser	Ala	cca Pro 1975	acc Thr	tgg Trp	ggc Gly	Thr	atc Ile 1980	ccc Pro	aaa Lys	ctg Leu	ccc Pro	5952
	cca cca Pro Pro 1985			Ser					Arg					Gln		6000
25	gca ata Ala Ile		Thr					Val					Ser			6048
30	gac ctg Asp Leu	Leu					Gly					Leu				6096
35	tac tct Tyr Ser					Ser					Gln					6144
40	agc cac Ser His 2050				Ser					Pro						6192
	ggc cca Gly Pro 2065			Asn					Pro					Ser		6240
45	tta gag Leu Glu		Asp					Trp					Leu			6288
50	cct ggc Pro Gly	Gly		Glu			Pro					Leu				6336
55	tac agc Tyr Ser					Ser					Pro					6384
60	gat gag Asp Glu 2130	cag Gln	agg Arg	aga Arg	His	tct Ser 2135	atc Ile	gcc Ala	gtc Val	Ser	tgc Cys 2140	ctg Leu	gac Asp	agc Ser	ggc Gly	6432
	tcc caa Ser Gln 2145	ccc Pro	cac His	Leu	ggc Gly 2150	aca Thr	gac Asp	ccc Pro	Ser	aac Asn 2155	ctt Leu	ggg Gly	ggc Gly	Gln	cct Pro 2160	6480

	ctt gg Leu Gl	A CJA a aaa	Pro	999 Gly 2165	agc Ser	cgg Arg	ccc	Lys	aaa Lys 2170	aaa Lys	ctc Leu	agc Ser	Pro	cct Pro 2175	agt Ser	6523
5	atc ac Ile Th	c ata r Ile	gac Asp 2180	ccc Pro	ccc Pro	gag Glu	Ser	caa Gln 2185	ggt Gly	cct. Pro	cgg Arg	Thr	ccg Pro 2190	ccc Pro	agc Ser	6576
10	cct gg Pro Gl	t atc y Ile 2195	Cys	ctc Leu	cgg Arg	Arg	agg Arg 2200	gct Ala	ccg Pro	tcc Ser	Ser	gac Asp 2205	tcc Ser	aag Lys	gat	6624
15	ccc tt Pro Le 221	u Ala	tct Ser	ggc Gly	Pro	cct Pro 2215	gac Asp	agc Ser	atg Met	Ala	gcc Ala 2220	tcg Ser	ccc Pro	tcc Ser	cca Pro	5672
20	aag aa Lys Ly 2225	a gat s Asp	gtg Val	Leu	agt Ser 2230	ctc Leu	tcc Ser	ggt Gly	Leu	tcc Ser 2235	tct Ser	gac Asp	cca Pro	Ala	gac Asp 2240	6720
20	ctg ga Leu As															6729
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30	<220> <221> <222>		(676:	2;			٠.									
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40	cgt ag Arg Se	c ttc r Phe	acg Thr 20	cag Gln	ctc Leu	aac Asn	gac Asp	ctg Leu 25	tcc Ser	ggg Gly	gcc Ala	ggg Gly	ggc Gly 30	cgg Arg	cag Gln	96
45	ggg cc Gly Pr	g ggg o Gly 35	tcg Ser	acg Thr	gaa Glu	aag Lys	gac Asp 40	ccg Pro	ggc Gly	agc Ser	gcg Ala	gac Asp 45	tcc Ser	gag Glu	gcg Ala	144
50	gag gg Glu Gl 5	y Leu	ccg Pro	tac Tyr	ccg Pro	gcg Ala 55	cta Leu	gcc Ala	ccg Pro	gtg Val	gtt Val 60	ttc Phe	ttc Phe	tac Tyr	ttg Leu	192
<b>50</b> .	agc ca Ser Gl 65															240
55	ccg tg Pro Tr	g ttc p Phe	gag Glu	cga Arg 85	gtc Val	agt Ser	atg Met	ctg Leu	gtc Val 90	att Ile	ctt Leu	ctc Leu	aac Asn	tgt Cys 95	gtg Val	288
60	act ct Thr Le	g ggt u Gly	atg Met 100	ttc Phe	agg Arg	ccg Pro	tgt Cys	gag Glu 105	gac Asp	att Ile	gcc Ala	tgt Cys	gac Asp 110	tcc Ser	cag Gln	336
	cgc tg Arg Cy	c cgg s Arg	atc Ile	ctg Leu	cag Gln	gcc Ala	ttc Phe	gat Asp	gac Asp	ttc Phe	atc Ile	ttt Phe	gcc Ala	ttc Phe	ttt Phe	384

			115					120					125				
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10								tgg Trp									480
10								tcg Ser									528
15	tcc Ser	gca Ala	gtc Val	agg Arg 180	aca Thr	gtc Val	cgt Arg	gtg Vạl	ctg Leu 185	cga Arg	ccg Pro	ctc Leu	agg Arg	gcc Ala 190	att Ile	aac Asn	576
20	cgg Arg	gtg Val	ccc Pro 195	agc Ser	atg Met	cgc Arg	att Ile	ctc Leu 200	gtc Val	aca Thr	tta Leu	ctg Leu	ctg Leu 205	gac Asp	acc Thr	ttg Leu	624
25	cct Pro	atg Met 210	ctg Leu	ggc Gly	aac Asn	gtc Val	ctg Leu 215	ctg Leu	ctc Leu	tgt Cys	ttc Phe	ttc Phe 220	gtc Val	ttt Phe	ttc Phe	atc	672
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35								gag Glu									816
40								aga Arg 280									864
45	cgt Arg	ggg Gly 290	gaa Glu	ggc Gly	ggt Gly	ggt Gly	ggc Gly 295	cca Pro	ccc Pro	tgc Cys	agt Ser	ctg Leu 300	gac Asp	tat Tyr	gag Glu	acc Thr	912
<i>50</i>								acc Thr									960
								cac His									1008
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60								atg Met 360									1104
	ttc Phe	tac Tyr	aac Asn	ttc Phe	atc Ile	tac Tyr	ttc Phe	att Ile	ctt Leu	ctc Leu	atc Ile	atc Ile	gtg Val	ggc Gly	tcc Ser	ttc Phe	1152

0.82

370

375

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10		tcc Ser															1296
15		gag Glu														gcc Ala	1344
20		agg Arg 450															1392
25		agc Ser														ggc Gly 480	1440
30		tgc .Cys		Arg													1488
	cac His	cat His	cac His	cac His 500	cac His	cat His	cac His	cac	tac Tyr 505	cac His	ctg Leu	ggt Gly	aat Asn	ggg Gly 510	acg Thr	ctc Leu	1536
35		gtt Val															1584
40		cgc Arg 530															1632
45		cct Pro															1680
50	tgc Cys	cac His	ttg Leu	gag Glu	cca Pro 565	gtc Val	cgt Arg	tgc Cys	cag Gln	gca Ala 570	ccc Pro	cct Pro	ccc Pro	aga Arg	tgc Cys 575	cca Pro	1728
		gag Glu															1776
<b>55</b>	gtg Val	cat His	acc Thr 595	agc Ser	cct Pro	cca Pro	cca Pro	gag Glu 600	ata Ile	ctg Leu	aag Lys	gat Asp	aaa Lys 605	gca Ala	cta Leu	gtg Val ·	1824
60	gag Glu	gtg Val 610	gcc Ala	ccc Pro	agc Ser	cct Pro	ggg Gly 615	ccc Pro	ccc Pro	acc Thr	ctc Leu	acc Thr 620	agc Ser	ttc Phe	aac Asn	atc Ile	1872
	cca Pro	cct Pro	Gly ggg	ccc Pro	ttc Phe	agc Ser	tcc Ser	atg Met	cac His	aag Lys	ctc Leu	ctg Leu	gag Glu	aca Thr	cag Gln	agt Ser	1920

	625			630			635			640	
5		gga Gly									1963
10		gac Asp									2016
10.		gga Gly									2064
15		agc Ser 690									2112
20		cgg Arg								gat Asp 720	2160
25		gag Glu									2208
<i>30</i>		cgg Arg									2256
		atc Ile									2304
35		gag Glu 770									2352
40		ctc Leu									2400
45		ggc Gly									2448
50		atc Ile									2496
		ctg Leu									2544
<i>55</i>		ccg Pro 850									2592
60		gtg Val									2640
		atc Ile									2688

					885					890					895		
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15									aac Asn								2880
20									cag Gln								2928
25	tct Ser	gag Glu	tca Ser	gag Glu 980	cct Pro	gat Asp	ttc Phe	ttt Phe	tcg Ser 985	ccc Pro	agt Ser	gtg Val	gat Asp	ggt Gly 990	gat Asp	ggg.	2976
30							Ala		gtg Val			Gly					3024
	Leu					Leu			ctc Leu		Ile					aca Thr	3072
35		Met			Pro				agc Ser	Thr					Āla		3120
40				Ser					agc Ser. 1					Glu			3168
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									egt Arg								3456

			:	1140				:	1145					1150			
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10	ggg Gly 1185	Arg			Arg	acc Thr 1190				Asp					Āsp		3600
15	gat Asp	gat Asp	gac Asp	Asn	gat Asp 1205	gag Glu	gga Gly	aat Asn	Leu	agc Ser 1210	aaa Lys	GJ À āāā	gaa Glu	Arg	ata Ile 1215	caa Gln	3648
20	gcc Ala		Val			cgg Arg		Pro					Glu		Asp		3696
25		Ser				ttt Phe	Pro					Phe					3744
<i>30</i>						His					His						3792
	atc Ile 1265	Phe			Cys	atc Ile 1270				Met					Ile		3840
35	ccc Pro			Ala		cgc Arg			Leu					Tyr			3888
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45	tgg Trp	Cys				cag Gln	Ala					Ser					3984
50	gac Asp 1					Leu					Asp						4032
	gtc Val 1345	Ser			Gly					Gly					Leu		4080
55	ctg Leu			Thr		cgt Arg			Arg					Ala			4128
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						tgc Cys											4224

	139	5	140		1405		
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10	acc agg aa Thr Arg As 1425	n Ile Thr	aac aaa to Asn Lys Se 430	er Asp Cys	gct gag gcc Ala Glu Ala 1435	age tac ega Ser Tyr Arg 1440	4320
	tgg gtc cg Trp Val Ar	g cac aag g His Lys 1445	tac aac tt Tyr Asn Ph	t gac aac ne Asp Asn 1450	ctg ggc cag Leu Gly Gln	gct ctg atg Ala Leu Met 1455	4368
15	tcc ctg tt Ser Leu Ph	t gtg ctg e Val Leu 1460	gcc tcc aa Ala Ser Ly	g gat ggt 's Asp Gly 1465	tgg gtt gac a	atc atg tat Ile Met Tyr 470	4416
20	gat ggg ct Asp Gly Le 147	u Asp Ala '	gtg ggt gt Val Gly Va 148	l Asp Gln	cag ccc atc a Gln Pro Ile N 1485	atg aac cac Met Asn His	4464
25	aac ccc tg Asn Pro Tr 1490	g atg ctg o	cta tac tto Leu Tyr Pho 1495	c atc tcc e Ile Ser	tto ctc ctc a Phe Leu Leu 1 1500	atc gtg gcc Ile Val Ala	4512
30	ttc ttt gte Phe Phe Va. 1505	l Leu Asn I	atg ttt gto Met Phe Vai 510	l Gly Val	gtg gtg gag a Val Val Glu <i>I</i> 515	aac ttc cat Asn Phe His 1520	4560
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35	aag cga cta Lys Arg Le	a cgg agg o 1 Arg Arg 1 1540	ctg gag aaa Leu Glu Lys	a aag aga s Lys Arg 1545	agg agt aag o Arg Ser Lys O 15	gag aag cag Slu Lys Gln 550	4656
40	atg gcc gaa Met Ala Glu 1555	ı Ala Gln (	tgc aag ccc Cys Lys Pro 1560	o Tyr Tyr	tct gac tac t Ser Asp Tyr S 1565	cg aga ttc Ser Arg Phe	4704
45	cgg ctc ctt Arg Leu Leu 1570	ı Val His H	cac ctg tgt His Leu Cys 1575	t acc agc s Thr Ser	cac tac ctg g His Tyr Leu A 1580	gac ctc ttc Asp Leu Phe	4752
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	gct att gtg Ala Ile Val	det etg t Leu Leu S	cc atc atg Ser Ile Met	g ggc atc a	aca ctg gag g Thr Leu Glu G	ag att gag lu Ile Glu	4992

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	atg cgg Met Arg	gca c Ala L 17	eu Leu	cac His	acg Thr	Val	atg Met 1705	cag Gln	gcc Ala	ctg Leu	Pro	cag Gln 1710	gtg Val	Gly ggg	5136
15	aac ctg Asn Leu	gga c Gly L 1715	tt ctc eu Leu	ttc Phe	Met	tta Leu 720	ttg Leu	ttt Phe	ttc Phe	Ile	ttt Phe 1725	gca Ala	gct Ala	ctg Leu	5184
20	ggc gtg Gly Val 1730	Glu L	tć ttt eu Phe	Gly A	gac Asp 735	ctg Leu	gag Glu	tgt Cys	Asp	gag Glu 740	aca Thr	cac His	cct Pro	tgt Cys	5232
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30	ctg acc Leu Thr	ctc t Leu P	tc cga he Arg 1765	gtc : Val :	tcc Ser	act Thr	Gly	gac Asp 1770	aac Asn	tgg Trp	aat Asn	Gly	att Ile 1775	atg Met	5328
	aag gac Lys Asp	acc c Thr L 17	eu Arg	gac (	tgt Cys	qzA	cag Gln .785	gag Glu	tcc Ser	acc Thr	Cys	tac Tyr 1790	aac Asn	act Thr	5376
35	gtc atc Val Ile	tcc c Ser P 1795	ct atc ro Ile	tac t Tyr 1	Phe	gtg Val .800	tcc Ser	ttc Phe	gtg Val	Leu	acg Thr 1805	gcc Ala	cag Gln	ttt Phe	5424
40	gtg ctg Val Leu 1810	Val A	ac gtg sn Val	Val :	ata Ile 815	gct Ala	gtg Val	ctg Leu	Met	aag Lys .820	cac His	ctg Leu	gaa Glu	gaa Glu	5472
45	agc aac Ser Asn 1825	aaa g Lys G	lu Ala	aag ( Lys ( 1830	gag Glu	gag Glu	gcc Ala	Glu	ctc Leu .835	gag Glu	gcc Ala	gag Glu	Leu	gag Glu 1840	5520
50	ctg gag Leu Glu	atg a Met L	ag acg ys Thr 1845	ctc a	agc Ser	ccg Pro	Gln	ccc Pro .850	cac His	tcc Ser	ccg Pro	Leu	ggc Gly 1855	agc Ser	5568
	ccc ttc Pro Phe		rp Pro			Glu					Thr				5616
<b>5</b> 5	aag cct Lys Pro	999 9 Gly A 1875	ct cca la Pro	cac a	Thr	act Thr 880	gcc Ala	cac His	att Ile	Gly	gca Ala 1885	gcc Ala	tcg Ser	ggc Gly	5664
60	ttc tcc Phe Ser 1890	Leu G	ag cac lu His	Pro :	acg Thr 895	atg Met	gta Val	ccc Pro	His	ccc Pro 900	gag Glu	gag Glu	gtg Val	cca Pro	5712
	gtc ccc Val Pro	cta g Leu G	ga cca ly Pro	gac ( Asp )	ctg Leu	ctg Leu	act Thr	gtg Val	agg Arg	aag Lys	tct Ser	ggt Gly	gtc Val	agc Ser	5760

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5	cgg acg cac Arg Thr His	tct ctg ccc aat Ser Leu Pro Asn 1925	gac agc tac atg tg Asp Ser Tyr Met Cy 1930	c cgc aat ggg agc 5808 s Arg Asn Gly Ser 1935
10	Thr Ala Glu	aga tcc cta gga Arg Ser Leu Gly 1940	cac agg ggc tgg gg His Arg Gly Trp Gl 1945	g ctc ccc aaa gcc 5856 y Leu Pro Lys Ala 1950
10	cag tca ggc Gln Ser Gly 1955	Ser Ile Leu Ser	gtt cac tcc caa cca Val His Ser Gln Pro 1960	a gea gae ace age 5904 o Ala Asp Thr Ser 1965
15	tgc atc cta Cys Ile Leu 1970	cag ctt ccc aaa Gln Leu Pro Lys 1975	gat gtg cac tat ctc Asp Val His Tyr Let 1980	Leu Gln Pro His
20	ggg gct ccc Gly Ala Pro 1985	acc tgg ggc gcc Thr Trp Gly Ala 1990	atc cct aaa cta ccc Ile Pro Lys Leu Pro 1995	c cca cct ggc cgc 6000 p Pro Pro Gly Arg 2000
25	tcc cct ctg Ser Pro Leu	gct cag agg cct Ala Gln Arg Pro 2005	ctc agg cgc cag gca Leu Arg Arg Gln Ala 2010	a gca ata agg act 6048 a Ala Ile Arg Thr 2015
30	Asp Ser Leu		ctg ggt agc cgg gas Leu Gly Ser Arg Gly 2025	
	gag gtg agt Glu Val Ser 2035	Gly Prc Ser Cys	cct stg acc cgg tcd Pro Leu Thr Arg Seg 2040	t tca tcc ttc tgg 6144 Ser Ser Phe Trp 2045
35	ggc ggg tcg Gly Gly Ser 2050	agc atc cag gtg Ser Ile Gln Val 2055	cag cag cgt tcc ggc Gln Gln Arg Ser Gly 2060	/ Ile Gln Ser Lys
40	gtc tcc aag Val Ser Lys 2065	cac atc cgc ctg His Ile Arg Leu 2070	cca gcc cct tgc cca Pro Ala Pro Cys Pro 2075	a ggc ctg gaa ccc 6240 o Gly Leu Glu Pro 2080
45			gag acc aga agc agc Glu Thr Arg Ser Ser 2090	
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		Phe Pro Arg Asp	ctg aag aag tgc tac Leu Lys Lys Cys Tyr 2120	
55			ggg ttc tgg cta gat Gly Phe Trp Leu Asp 2140	Glu Gln Arg Arg
60	cac tcc att His Ser Ile 2145	gct gtc agc tgt Ala Val Ser Cys 2150	ctg gac agc ggc tcc Leu Asp Ser Gly Ser 2155	c caa ccc cgc cta 6480 c Gln Pro Arg Leu . 2160
			ggg ggc caa cct ctt Gly Gly Gln Pro Lev	

		2165			2170		2175	
5	ago ogg od Ser Arg Pr	t aag aaa o Lys Lys 2180	aaa oto Lys Leu	age cca Ser Pro 2185	ccc agt Pro Ser	atc tct ata Ile Ser Ile 2190	Asp Pro	6576
10	ccg gag ag Pro Glu Se 219	r Gln Gly	Ser Arg	ccc cca Pro Pro 2200	tgc agt Cys Ser	oot ggt gto Pro Gly Val 2205	tgc ctc Cys Leu	6624
10	agg agg ag Arg Arg Ar 2210	g gcg ccg g Ala Pro	gcc agt Ala Ser 2215	gac tot Asp Ser	Lys Asp	ccc tcg gtc Pro Ser Val 220	tcc agc Ser Ser	6672
15	ccc ctt ga Pro Leu As 2225	p Ser Thr	gct gcc Ala Ala 2230	tca ccc Ser Pro	tcc cca Ser Pro 2235	aag aaa gac Lys Lys Asp	acg ctg Thr Leu 2240	6720
20	agt ctc tc Ser Leu Se	t ggt ttg r Gly Leu 2245	tct tct Ser Ser	Asp Pro	aca gac Thr Asp 2250	atg gas cco Met Asp Pro		6762
25	<210> 6 <211> 6795 <212> DNA <213> Ratt						•	
30	<220> <221> CDS <222> (1).	. (6795)						
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40	cgt agc tt Arg Ser Ph	c acg cag e Thr Gln 20	ctc aac Leu Asn	gac ctg Asp Leu 25	tcc ggg	gcc ggg ggc Ala Gly Gly 30	Arg Gln	96
45	Gly Pro Gl	g tcg acg y Ser Thr 5	gaa aag Glu Lys	gac ccg Asp Pro 40	ggc agc ( Gly Ser )	gcg gac tcc Ala Asp Ser 45	gag gcg Glu Ala	144
	gag ggg ct Glu Gly Le 50	g ccg tac u Pro Tyr	ccg gcg Pro Ala 55	cta gcc Leu Ala	ccg gtg ( Pro Val	gtt ttc ttc Val Phe Phe 60	tac ttg Tyr Leu	192
50	agc cag ga Ser Gln As 65	c agc cgc p Ser Arg	ccg cgg Pro Arg 70	agc tgg Ser Trp	tgt ctc ( Cys Leu 7 75	cgc acg gtc Arg Thr Val	tgt aac Cys Asn 80	240
<i>55</i>	ccg tgg tt Pro Trp Ph	c gag cga e Glu Arg 85	gtc agt Val Ser	atg ctg Met Leu	gtc att ( Val Ile 1 90	ctt ctc aac Leu Leu Asn	tgt gtg Cys Val 95	288
60	act ctg gg Thr Leu Gl	t atg ttc y Met Phe 100	agg ccg Arg Pro	tgt gag Cys Glu 105	gac att o	gcc tgt gac Ala Cys Asp 110	tcc cag Ser Gln	336
	cgc tgc cg Arg Cys Ar 11	g Ile Leu	cag gcc Gln Ala	ttc gat Phe Asp 120	gac ttc ( Asp Phe	atc ttt gcc Ile Phe Ala 125	ttc ttt Phe Phe	384

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J	aaa Lys 145	tgt Cys	tac Tyr	ctg Leu	gga Gly	gac Asp 150	act Thr	tgg Trp	aac Asn	cgg Arg	ctt Leu 155	gac Asp	ttt Phe	ttc Phe	att Ile	gtc Val 160	480
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15	tcc Ser	gca Ala	gtc Val	agg Arg 180	aca Thr	gtc Val	cgt Arg	gtg Val	ctg Leu 185	cga Arg	ccg Pro	ctc Leu	agg Arg	gcc Ala 190	att	aac Asn	576
20	cgg Arg	gtg Val	ccc Pro 195	agc Ser	atg Met	cgc Arg	att Ile	ctc Leu 200	gtc Val	aca Thr	tta Leu	ctg Leu	ctg Leu 205	gac Asp	acc Thr	ttg Leu	624
25				ggc Gly													672
				gtg Val													720
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35	cct Pro	tat Tyr	tac Tyr	cag Gln 2 <u>6</u> 0	aca Thr	gag Glu	aat Asn	gag Glu	gac Asp 265	gag Glu	agc Ser	ccc Pro	ttc Phe	atc Ile 270	tgc Cys	tct Ser	816
40	cag Gln	cct	cgg Arg 275	gag Glu	aat Asn	ggc Gly	atg Met	aga Arg 280	tcc Ser	tgc Cys	agg Arg	agt Ser	gtg Val 285	ccc Pro	aca Thr	ctg Leu	864
45	cgt Arg	999 Gly 290	gaa Glu	ggc Gly	ggt Gly	ggt Gly	ggc Gly 295	cca Pro	ccc Pro	tgc Cys	agt Ser	ctg Leu 300	gac Asp	tat Tyr	gag Glu	acc Thr	.912
				tcc Ser													960
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				ttc Phe													1152

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J			cag Gln													ttc Phe	1248
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15	tat Tyr	gag Glu	gag Glu 435	cta Leu	ctc Leu	aag Lys	tac Tyr	ctg Leu 440	gtg Val	tac Tyr	atc Ile	ctc Leu	cga Arg 445	aaa Lys	gca Ala	gcc Ala	1344
20	cga Arg	agg Arg 450	ctg Leu	gcc Ala	cag Gln	gtc Val	tct Ser 455	agg Arg	gct Ala	ata Ile	Gly	gtg Val 460	cgg Arg	gct Ala	ggg Glý	ctg Leu	1392
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	agc Ser	tgc Cys	act Thr	cgc Arg	tca Ser 485	cac His	cgt Arg	cgt Arg	ctg Leu	tct Ser 490	gtc Val	cac His	cac His	ctg Leu	gtc Val 495	cac His	1488
30			cac His														1536
35	aga Arg	gtt Val	ccc Pro 515	cgg Arg	gcc Ala	agc Ser	cca Pro	gag Glu 520	atc Ile	cag Gln	gac Asp	agg Arg	gat Asp 525	gcc Ala	aat Asn	Gly ggg	1584
40			cgg Arg														1632
45			ccg Pro														1680
			ttg Leu														1728
50			gca Ala														1776
55			acc Thr 595														1824
60			gcc Ala														1872
	cca Pro 625	cct Pro	ggg Gly	ccc Pro	ttc Phe	agc Ser 630	tcc Ser	atg Met	cac His	aag Lys	ctc Leu 635	ctg. Leu	gag Glu	aca Thr	cag Gln	agt Ser 640	1920

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	gca Ala	gad Asp	agt Ser	gga Gly 660	'Ala	tgc Cys	: ggg	r CCG	gac Asp 665	Ser	tgt Cys	ccc Pro	tac Tyr	tgt Cys 670	Ala	cgg Arg	2016
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15	gac Asp	ago Ser 690	Glu	gct Ala	gtg Val	tat Tyr	gag Glu 695	Phe	aca Thr	cag Gln	gac Asp	gct Ala 700	Gln	cac His	agt Ser	gac	2112
20	ctc Leu 705	Arg	gat Asp	ccc Pro	cac His	agc Ser 710	cgg Arg	cgg Arg	cga Arg	cag Gln	cgg Arg 715	Ser	ctg Leu	GŢĀ	cca Pro	gat Asp 720	2160
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	ttc Phe	cgg Arg	aag Lys	atc Ile 740	gta Val	gat Asp	agc Ser	aaa Lys	tac Tyr 745	ttt Phe	Gly	cgg Arg	gga Gly	atc Ile 750	atg Met	atc Ile	2256
·30	gcc Ala	atc Ile	ctg Leu 755	vaı	aat Asn	aca Thr	ctc Leu	agc Ser 760	atg Met	ggc Gly	atc Ile	gag Glu	tac Tyr 765	cac His	gag Glu	cag Gln	2304
35	ccc Pro	gag Glu 770	gag Glu	ctc Leu	acc Thr	aac Asn	gcc Ala 775	ctg Leu	gaa Glu	atc Ile	agc Ser	aac Asn 780	atc Ile	gtc Val	ttc Phe	acc Thr	2352
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	gcc Ala	atc Ile	gtc Val 915	act Thr	gtc Val	ttt Phe	cag Gln	att Ile 920	ctg Leu	act Thr	cag Gln	gaa Glu	gac Asp 925	Trp Tgg	aat Asn	aaa Lys	2784
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15					atg Met												2880
20					gtg Val 965												2928
25					cct Pro												2976
	gac Asp	aga Arg	aag Lys 995	aag Lys	cgc Arg	ttg Leu	Ala	ctg Leu 1000	gtg Val	gct Ala	ttg Leu	Gly	gaa Glu 1005	cac His	gcg Ala	gaa Glu	3024
30	Leu				ctt Leu	Leu					Ile						3072
35	cca Pro 1025	Met	tca Ser	cac His	ccc Pro	aag Lys 1030	agc Ser	tcc Ser	agc Ser	Thr	ggt Gly LO35	gtg Val	ggg Gly	gaa Glu	Ala	ctg Leu 1040	3120
40				Ser	cga Arg 1045				Ser					Glu			3168
45			His		gag Glu			Cys					Arg				3216
	cac His	Ser	ccc Pro 1075	tgg Trp	agt Ser	gcg Ala	Ala	agc Ser 1080	agc Ser	tgg Trp	acc Thr	Ser	agg Arg 1085	cgc Arg	tcc Ser	agc Ser	3264
50	Arg				ggc Gly	Arg					Lys						3312
55	ggg Gly 110	Glu	cgg Arg	agg Arg	tcc Ser	ctg Leu l110	ctg Leu	tct Ser	gga Gly	Glu	ggc Gly L115	cag Gln	gag Glu	agt Ser	Gln	gat Asp 1120	<b>336</b> 0
60				Ser	tca Ser 1125				Arg					Gly			3408
	cat His	cgc Arg	His	agg Arg 1140	ggt Gly	tcc Ser	ttg Leu	Glu	cgt Arg 1145	gag Glu	gcc Ala	aag Lys	Ser	tcc Ser L150	ttt Phe	gac Asp	3456

5	ct: Le:	g co i Pro	t gad o Asp 1155	Thi	t ctq Leu	r cag i Gln	g gtg Val	pro Pro 1160	G1;	j ctg / Leu	g cac His	cgc Arc	aca g Thr 1165	Ala	c ago	ggc Gly	3504
	ogq Arq	g age ; Se: 1170	r Ser	gcc Ala	tot Ser	gag Glu	cac His	Gln	gac Asp	tgt Cys	Asn	ggc Gly 1180	/ Lys	tc; Se:	g got Ala	tca Ser	3552
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20	gcc Ala	tgç Trp	) Val	aga Arg 1220	Ser	cgg Arg	ctt Leu	Pro	gcc Ala 1225	Cys	tgc Cys	cga Arg	Glu	cga Arg 1230	Asp	tcc Ser	3696
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, <b>3</b> 0 -	atc Ile 126	Phe	ctc Leu	aac Asn	Cys	atc Ile 1270	acc Thr	atc Ile	gct Ala	Met	gag Glu 1275	cgc Arg	ccc Pro	aaa Lys	Ile	gac Asp 1280	3840
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	Asp	ggc Gly 1330	ttg Leu	ctg Leu	gtg Val	Leu	atc Ile .335	tcc Ser	gtc Val	atc Ile	Asp	atc Ile 340	ctg Leu	gtc Vai	tcc Ser	atg Met	4032
50	gtc Val 1345	Ser	gac Asp	agc Ser	Gly	acc Thr 350	aag Lys	atç Ile	ctt Leu	Gly	atg Met 355	ctg Leu	agg Arg	gtg Val	Leu	cgg Arg 360	4080
55	ctg Leu	ctg Leu	cgg Arg	Thr	ctg Leu .365	cgt Arg	cca Pro	ctc Leu	Arg	gtc Val 370	atc Ile	agc Ser	cgg Arg	Ala	cag Gln 1375	gga Gly -	4128
60	ctg Leu	aag Lys	ctg Leu 1	gtg Val 380	gta Väl	gag Glu	act Thr	Leu	atg Met 385	tca Ser	tcc Ser	ctc Leu	Lys	ccc Pro 390	att Ile	ggc Gly	4176
	aac Asn	TTE	gtg Val 1395	gtc Val	att Ile	tgc Cys	Cys .	gcc Ala 400	ttc Phe	ttc Phe	atc Ile	Ile	ttt Phe 405	gga Gly	att Ile	ctc Leu	4224

5	ggg gtg cag ctc ttc aaa ggg aag ttc ttc gtg tgt cag ggt gag gac Gly Val Gln Leu Phe Lys Gly Lys Phe Phe Val Cys Gln Gly Glu Asp 1410 1415 1420	4272
-	acc agg aac atc act aac aaa too gac tgo got gag goo ago tao oga Thr Arg Asn Ile Thr Asn Lys Ser Asp Cys Ala Glu Ala Ser Tyr Arg 1425 1430 1435 1440	4320
10	tgg gtc cgg cac aag tac aac ttt gac aac ctg ggc cag gct ctg atg Trp Val Arg His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met 1445 1450 1455	4368
15	tcc ctg ttt gtg ctg gcc tcc aag gat ggt tgg gtt gac atc atg tat Ser Leu Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asp Ile Met Tyr 1460 1465 1470	4416
20	gat ggg ctg gat gct gtg ggt gtg gat cag cag ccc ate atg aac cac Asp Gly Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His 1475 1480 1485	4464
25	aac ccc tgg atg ctg cta tac ttc atc tcc ttc ctc ctc atc gtg gcc Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ala 1490 1495 1500	4512
23	ttc ttt gtc ctg aac atg ttt gtg ggc gtg gtg gtg gag aac ttc cat Phe Phe Val Leu Asn Met Phe Val Gly Val Val Glu Asn Phe His 1505 1510 1515 1520	4560
30	aag tgc aga cag cac cag gag gag gag gag gcg agg cgg c	4608
35	aag cga cta cgg agg ctg gag aaa aag aga agg aat cta atg ttg gac Lys Arg Leu Arg Arg Leu Glu Lys Lys Arg Arg Asn Leu Met Leu Asp 1540 1545 1550	4656
40	gat gta att gct tcc ggc agc tca gcc agc gct gcg tca gaa gcc cag Asp Val Ile Ala Ser Gly Ser Ser Ala Ser Ala Ala Ser Glu Ala Gln 1555 1560 1565	4704
45	tgc aag ccc tac tac tct gac tac tcg aga ttc cgg ctc ctt gtc cac Cys Lys Pro Tyr Tyr Ser Asp Tyr Ser Arg Phe Arg Leu Leu Val His 1570 1575 1580	4752
	cac ctg tgt acc agc cac tac ctg gac ctc ttc atc act ggt gtc atc His Leu Cys Thr Ser His Tyr Leu Asp Leu Phe Ile Thr Gly Val Ile 1585 1590 1595 1600	4800
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55	atc ctg gac gag gct ctg aag atc tgc aat tac atc ttt acc gtc atc Ile Leu Asp Glu Ala Leu Lys Ile Cys Asn Tyr Ile Phe Thr Val Ile 1620 1625 1630	4896
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	ttc ttc cag gac agg tgg aac cag ctg gac ctg gct att gtg ctt ctg Phe Phe Gln Asp Arg Trp Asn Gln Leu Asp Leu Ala Ile Val Leu Leu 1650 1655 1660	4992

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	ece Pro	atc Ile	aac Asn	Pro	acc Thr 1685	atc Ile	atc Ile	cgt Arg	Ile	atg Met 1690	agg Arg	gtg Val	ctc Leu	Arg	att Ile 1695	gct Ala	5088
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25	gga Gly 1745	Asp	ctg Leu	gag Glu	Cys	gat Asp 1750	gag <sup>.</sup> Glu	aca Thr	cac His	Pro	tgt Cys .755	gag Glu	ggc Gly	ttg Leu	Gly	cgg Arg L760	5280
	cat His	gcc Ala	acc Thr	Phe	agg Arg 1765	aac Asn	ttt Phe	ggt Gly	Met	gcc Ala 1770	ttt Phe	ctg Leu	acc Thr	Leu	ttc Phe 1775	cga Arg	5328
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	aag Lys	gag: Glu	gag Glu	Ala	gag Glu .845	ctc Leu	gag Glu	gcc Ala	Glu	ctg Leu .850	gag Glu	ctg Leu	gag Glu	Met	aag Lys 1855	acg Thr	5568
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60	His	acc Thr 890	act Thr	gcc; Ala	cac His	att Ile 1	gga, Gly .895	gca <sup>r</sup> Ala	gcc Ala	tcg Ser	Gly	ttc Phe 900	tcc Ser	ctt Leu	gag Glu	cac His	5712
	ccc Pro 1905	Thr	atg. Met	gta Val	Pro	cac His 1910	Pro-	gag Glu	gag Glu	Val	cca Pro 915	gtc Val	ccc Pro	cta Leu	Gly	cca Pro .920	5760

<i>5</i>		Leu Thr V				agc cgg ac Ser Arg Ti		
	ccc aat o Pro Asn A	gac agc t Asp Ser 1 1940	ac atg t Yr Met C	ys Arg A	aat ggg Asn Gly 945	ago act go Ser Thr Al	t gag aga a Glu Arg 1950	tcc 5856 Ser
10	Leu Gly H	cac agg o His Arg 0 955	ggo tgg g Sly Trp G	gg ctc c ly Leu E 1960	ecc aaa Pro Lys	gcc cag to Ala Gln Se 196	er Gly Ser	atc 5904 Ile
15	ttg tcc c Leu Ser V 1970	gtt cac t Val His S	cc caa c Ser Gln P 19	ro Ala A	gac acc Asp Thr	agc tgc at Ser Cys Il 1980	c cta cag e Leu Gln	ctt 5952 Leu
20					Gln Pro	cat ggg go His Gly Al 995	a Pro Thr	
25		Ile Pro I				cgc tcc co Arg Ser Pr		
	agg cct o Arg Pro I	Leu Arg A 2020	gc cag g Arg Gln A	la Ala I	ita agg le Arg )25	act gac to Thr Asp Se	c ctg gat er Leu Asp 2030	gtg 6096 Val
30	Gln Gly I	ctg ggt a Leu Gly S )35	igc cgg g Ser Arg G	aa gac c lu Asp I 2040	etg ttg Leu Leu	tca gag gt Ser Glu Va 204	l Ser Gly	ccc 6144 Pro
35	tcc tgc c Ser Cys E 2050	cct ctg a Pro.Leu T	icc cgg t Thr Arg S 20	er Ser S	cc ttc Ser Phe	tgg ggc gg Trp Gly Gl 2060	g tcg agc y Ser Ser	atc 6192 Ile
40					31n Ser	aaa gtc to Lys Val Se 075	r Lys His	
45		Pro Ala P				ccc agc to Pro Ser Tr		
				er Leu G		gac acg ga Asp Thr Gl		
50	Ile Ser C					gaa gaa co Glu Glu Pr 212	o Leu Phe	
55				yr Ser V		acc cag ac Thr Gln Se 2140		
60					Sln Arg	aga cac to Arg His Se 155	r Ile Ala	
	agc tgt o Ser Cys I	Leu Asp S	ige gge t Ser Gly S .65	cc caa c er Gln F	ecc cgc Pro Arg 2170	cta tgt co Leu Cys Pr	a age cee to Ser Pro 2175	tca 6528 Ser

يو.	age etc ggg ggs caa cet ett ggg ggt eet ggg ags egg eet aag aaa Ser Leu Gly Gly Gln Pro Leu Gly Gly Pro Gly Ser Arg Pro Lys Lys 2180 2185 2190	6576
5	aaa ctc agc cca ccc agt atc tct ata gac ccc ccg gag agc cag ggc Lys Leu Ser Pro Pro Ser Ile Ser Ile Asp Pro Pro Glu Ser Gln Gly 2195 2200 2205	6624
10	tot egg eec eea tge agt eet ggt gte tge etc agg agg agg geg eeg Ser Arg Pro Pro Cys Ser Pro Gly Val Cys Leu Arg Arg Arg Ala Pro 2210 2215 2220	6672
15	god agt gad tot aag gat dod tog gto tod agd dod ott gad agd adg Ala Ser Asp Ser Lys Asp Pro Ser Val Ser Ser Pro Leu Asp Ser Thr 2225 2230 2235	6720
20	got god toa ood tod ooa aag aaa gad acg otg agt otd tot ggt ttg Ala Ala Ser Pro Ser Pro Lys Lys Asp Thr Leu Ser Leu Ser Gly Leu 2245 2250 2255	6768
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40	cgt agc ttc acg cag ctc aac gac ctg tcc ggg gcc ggg ggc cgg cag Arg Ser Phe Thr Gin Leu Asn Asp Leu Ser Gly Ala Gly Gly Arg Gln 20 25 30	96
45	ggg ccg ggg tcg acg gaa aag gac ccg ggc agc gcg gac tcc gag gcg Gly Pro Gly Ser Thr Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala 35 40 45	144
50	gag ggg ctg ccg tac ccg gcg cta gcc ccg gtg gtt ttc ttc tac ttg Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu 50 60	192
<i>55</i>	age cag gae age ege eeg egg age tgg tgt ete ege aeg gte tgt aac Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn 65 70 75 80	240
	ccg tgg ttc gag cga gtc agt atg ctg gtc att ctt ctc aac tgt gtg Pro Trp Phe Glu Arg Val Ser Met Leu Val Ile Leu Leu Asn Cys Val 85 90 95	288
60	act ctg ggt atg ttc agg ccg tgt gag gac att gcc tgt gac tcc cag Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln 100 105 110	336

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10											ctt Lėu 155						480
15											ctg Leu						528
20	tcc Ser	gca Ala	gtc Val	agg Arg 180	aca Thr	gtc Val	cgt Arg	gtg Val	ctg Leu 185	cga Arg	ccg Pro	ctc Leu	agg Arg	gcc Ala 190	att Ile	aac Asn	576
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30											gga Gly 235						720
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40											agc Ser						816
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- •	ctg Leu	gag Glu	ggc Gly 355	tgg Trp	gtc Val	gac Asp	atc Ile	atg Met 360	tac Tyr	ttc Phe	gta Val	atg Met	gac Asp 365	gct Ala	cac His	tcc Ser	1104

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50	tgc Cys	cac His	ttg Leu	gag Glu	cca Pro 565	gtc Val	cgt Arg	tgc Cys	cag Gln	gca Ala 570	ccc Pro	cct Pro	ccc Pro	aga Arg	tgc Cys 575	cca Pro	1728
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60	gag Glu	gtg Val 610	gcc Ala	ccc Pro	agc Ser	cct Pro	ggg Gly 615	ccc Pro	ccc Pro	acc Thr	ctc Leu	acc Thr 620	agc Ser	ttc Phe	aac Asn	atc Ile	1872

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5	acg Thr	gga Gly	gcc Ala	tgc Cys	Cat His 645	Ser	Ser	tgc Cys	: aaa : Lys	ato Ile 650	Ser	ago Ser	Pro	tgc Cys	Ser 655	aag Lys	1968
10	Ата	Asp	ser	660	Ala	Cys	СīУ	Pro	Asp 665	Ser	Cys	Pro	Tyr	Cys 670	Ala	cgg Arg	2016
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2.5	705	Arg	Asp	Pro	His	Ser 710	Arg	Arg	Arg	Gln	Arg 715	agc Ser	Leu	Gly	Pro	Asp 720	2160
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10					gtc Val												2784
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	gat ggg ctg gat gct gtg ggt gtg gat cag cag ccc atc atg aac cac Asp Gly Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His 1475 1480 1485	4464
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	aat tac atc ttt acc gtc atc ttt gtc ttt gag tca gtt ttc aaa ctt Asn Tyr Ile Phe Thr Val Ile Phe Val Phe Glu Ser Val Phe Lys Leu 1635 1640 1645	4944

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25	cct cat ggg gct ccc acc tgg ggc gcc atc cct aaa cta ccc cca cct Pro His Gly Ala Pro Thr Trp Gly Ala Ile Pro Lys Leu Pro Pro 2005 2010 2015	6048
30	ggc cgc tcc cct ctg gct cag agg cct ctc agg cgc cag gca gca ata Gly Arg Ser Pro Leu Ala Gln Arg Pro Leu Arg Arg Gln Ala Ala Ile 2020 2025 2030	6096
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	cgg Arg	aga Arg	cac His	Ser	att Ile 2165	gct Ala	gtc Val	agc Ser	Cys	ctg Leu 2170	gac Asp	agc Ser	GJ. ggs	too Ser	caa Gln 2175	ccc	6528
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20	tgc Cys 222	Leu	agg Arg	agg Arg	Arg	gcg Ala 2230	ccg Pro	gcc Ala	agt Ser	Asp	tct Ser 2235	aag Lys	gat Asp	ccc Pro	Ser	gtc Val 2240	6720
	tcc Ser	agc Ser	ccc Pro	Leu	gac Asp 2245	agc Ser	acg Thr	gct Ala	Ala	tca Ser 2250	ccc Pro	tcc Ser	cca Pro	Lys	aaa Lys 2255	gac Asp	6768
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	<21			s sp													
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35 40	<220 <221 <222 <400 atg	3> Ra 0> 1> C1 2> () 0> 8 gac	os l)	(674) gag	l) gag	gat Asp	gga Gly	gcg Ala	ggc Gly	gcc Ala 10	gag Glu	gag Glu	tcg Ser	gga Gly	cag Gln 15	ccc Pro	48
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50					ggt Gly												1680
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					ggt Gly												1776
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20						tat Tyr											2112
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						aca Thr											230.4
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						cgc Arg											2544
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	Leu 1 2145	qzA	Ser	Gly		Gln 2150	Pro	Arg	Leu	-	Pro 2155	Ser	Pro	Ser		Leu 2160	
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15	ccc o	Pro					Val					Arg					6624
15	gac t Asp 3					Ser					Leu						6672
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				·	-												
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35 40	<220 <221	> > CD > (1 > 9 acc	)s .)( gag	(6132 ggc	gca	cgg Arg	gcc Ala	gcc Ala	gac Asp	gag Glu 10	gtc Val	cgg Arg	gtg Val	ccc Pro	ctg Leu 15	gly ggg	48
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10	ggc aag Gly Lys 1170	ggc a Gly S	gc acc er Thr	Asp .	gac ( Asp ( 175	gaa ( Glu /	gct Ala	gag Glu	Asp	ggc Gly 180	agg Arg	gcg Ala	cgc Arg	tcc Ser	3552
15	ggg ccc Gly Pro 1185		la Thr					Ala					Pro		3600
20	ccc ctg Pro Leu						Tyr					Arg			3648
25	cag gtg Gln Val	Val A				Asp !					Ile				3696
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	gac att Asp Ile														4176

		1380		1385	1390	
5	gtt ctg co Val Leu A	rg Val Leu	cgt ctg ct Arg Leu Le 140	eu Arg Thr L	etg egg eet etg Leu Arg Pro Leu 1405	agg gtc 4224 Arg Val
10	atc agc co Ile Ser A: 1410	gg gcc ccg rg Ala Pro	ggc ctc as Gly Leu Ly 1415	ag ctg gtg g ys Leu Val V	gtg gag acg ctg Val Glu Thr Leu 1420	ata tca 4272 Ile Ser
10	tca ctc ad Ser Leu A: 1425	rg Pro Ile	ggg aac at Gly Asn Il 1430	le Val Leu I	tc tgc tgc gcc le Cys Cys Ala 35	ttc ttc 4320 Phe Phe 1440
15	atc att to	tt ggc att he Gly Ile 1445	ttg ggt gt Leu Gly Va	tg cag ctc t al Gln Leu P 1450	tc aaa ggg aag Phe Lys Gly Lys 1	ttc tac 4368 Phe Tyr 455
20	tac tgc ga Tyr Cys G	ag ggc ccc lu Gly Pro 1460	gac acc ac Asp Thr Ar	gg aac atc t rg Asn Ile S 1465	cc acc aag gca Ser Thr Lys Ala 1470	cag tgc 4416 Gln Cys
25	cgg gcc gc Arg Ala A	la His Tyr	cgc tgg gt Arg Trp Va 148	al Arg Arg L	ag tac aac ttc ys Tyr Asn Phe 1485	gac aac 4464 Asp Asn
30	ctg ggc c Leu Gly G 1490	ag gcc ctg ln Ala Leu	atg tcg ct Met Ser Le 1495	tg ttc gtg c eu Phe Val L	etg tca tcc aag Leu Ser Ser Lys 1500	gat gga 4512 Asp Gly
	tgg gtg a Trp Val A 1505	sn Ile Met	tac gac go Tyr Asp Gl 1510	ly Leu Asp A	gcc gtg ggt gtc Ma Val Gly Val 15	gac cag 4560 Asp Gln 1520
35	cag cct g Gln Pro V	tg cag aac al Gln Asn 1525	cac aac co His Asn Pr	cc tgg atg c ro Trp Met I 1530	etg ctg tac ttc Leu Leu Tyr Phe 1	atc tcc 4608 Ile Ser 535
40	ttc ctg c Phe Leu L	tc atc gtc eu Ile Val 1540	agc ttc tt Ser Phe Ph	tc gtg ctc a he Val Leu A 1545	ac atg ttc gtg Asn Met Phe Val 1550	ggc gtc 4656 Gly Val
45	gtg gtc g Val Val G 15	lu Asn Phe	cac aag to His Lys Cy 156	ys Arg Pro H	cac cag gag gcg His Gln Glu Ala 1565	gag gag 4704 Glu Glu
50	gcg cgg c Ala Arg A 1570	gg cga gag rg Arg Glu	gag aag co Glu Lys Ar 1575	gg ctg cgg c rg Leu Arg A	egc cta gag agg Arg Leu Glu Arg 1580	agg cgc 4752 Arg Arg
	agg agc a Arg Ser T 1585	hr Phe Pro	agc cca ga Ser Pro Gl 1590	lu Ala Gln A	ege egg eee tae Arg Arg Pro Tyr 195 ·	tat gcc 4800 Tyr Ala 1600
<b>5</b> 5	gac tac t Asp Tyr S	cg ccc acg er Pro Thr 1605	cgc cgc to Arg Arg Tr	gg att cac t rp Ile His S 1610	cg ctg tgc acc Ser Leu Cys Thr 1	agc cac 4848 Ser His 615
60	tat ctc g Tyr Leu A	ac ctc ttc sp Leu Phe 1620	atc acc to Ile Thr Ph	tc atc atc t he Ile Ile C 1625	gt gtc aac gtc Cys Val Asn Val 1630	atc acc 4896 Ile Thr
	atg tcc a Met Ser M	tg gag cac let Glu His	tat aac ca Tyr Asn G	aa ccc aag t ln Pro Lys S	ccg ctg gac gag Ser Leu Asp Glu	gcc ctc 4944 Ala Leu

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5	aag t Lys T 16	ac Syr 550	tgc Cys	aac Asn	tac Tyr	Val	ttc Phe 1655	acc Thr	atc Ile	gtg Val	Phe	gtc Val 1660	ttc Phe	gag Glu	gct Ala	gca Ala	4992
10	ctg a Leu L 1665	ag ys	ctg Leu	gta Val	Ala	ttt Phe 1670	Gj À aaa	ttc Phe	Arg ogt	Arg	ttc Phe 1675	ttc Phe	aag Lys	gac Asp	Arg	tgg Trp 1680	5040
	aac c Asn G	ag iln	ctg Leu	Asp	ctg Leu 1685	gcc Ala	atc Ile	gtg Val	Leu	ctg Leu 1690	tca Ser	ctc Leu	atg Met	Gly	atc Ile 1695	acg Thr	5088
15	ctg g Leu G	ag ilu	Glu	ata Ile 1700	gag Glu	atg Met	agc Ser	Ala	gcg Ala 1705	ctg Leu	ccc Pro	atc Ile	Asn	ccc Pro 1710	acc Thr	atc Ile	5136
20	atc c Ile A	rg	atc Ile 715	atg Met	cgc Arg	gtg Val	Leu	cgc Arg 1720	att Ile	gcc Ala	cgt Arg	Val	ctg Leu 1725	aag Lys	ctg Leu	ctg Leu	5184
25	aag a Lys M 17	tg let 30	gct Ala	acg Thr	ggc Gly	Met	cgc Arg 1735	gcc Ala	ctg Leu	ctg Leu	Asp	act Thr 1740	gtg Val	gtg Val	caa Gln	gct Ala	5232
30	ctc c Leu P 1745	cc ro	cag Gln	gtg Val	Gly	aac Asn 1750	ctg Leu	ggc Gly	ctt Leu	Leu	ttc Phe 755	atg Met	ctc Leu	ctg Leu	Phe	ttt Phe L760	5280
	atc t Ile T	at yr	gct Ala	Ala	ctg Leu .765	gga Gly	gtg Val	gag Glu	Leu	ttc Phe 1770	Gly	agg Arg	ctg Leu	Glu	tgc Cys 1775	agt Ser	5328
35	gaa g Glu A	ac sp	Asn	ccc Pro 780	tgc Cys	gag Glu	ggc Gly	Leu	agc Ser 785	agg Arg	cac His	gcc Ala	Thr	ttc Phe 1790	agc Ser	aac Asn	5376
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50	aag c Lys H 1825	ac is	tgc Cys	ctg Leu	Ser	tac Tyr .830	ctg Leu	ccg Pro	gcc Ala	Pro	tcg Ser 835	ccc Pro	gtc Val	tac Tyr	Phe	gtg Val .840	5520
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<i>55</i>	gtg c Val L	tc eu l	Met	aag Lys 860	cac His	ctg Leu	gag Glu	Glu	agc Ser 865	aac Asn	aag Lys	gag Glu	Ala	cgg Arg .870	gag Glu	gat Asp	5616
60	gcg g Ala G	lu :	ctg Leu 875	gac Asp	gcc Ala	gag Glu	Ile	gag Glu 880	ctg Leu	gag Glu	atg Met	Ala	cag Gln .885	ggc Gly	ccc. Pro	GJ Å āāā	5664
	agt g	ca la	cgc Arg	cgg Arg	gtg Val	gac Asp	gcg Ala	gac Asp	agg Arg	cct Pro	ccc Pro	ttg Leu	ccc Pro	cag Gln	gag Glu	agt Ser	5712

	1890	· 1	8 9 5	1900		
5	ccg ggc gcc Pro Gly Ala 1905	agg gac gcc Arg Asp Ala 1910	cca aac ctg Pro Asn Leu	gtt gca cgc Val Ala Arg 1915	aag gtg toc gtg Lys Val Ser Val 1920	5760
10	tcc agg atg Ser Arg Met	ctc tcg ctg Leu Ser Leu 1925	Pro Asn Asp	agc tac atg Ser Tyr Met 1930	tte agg eee gtg Phe Arg Pro Val 1935	5808
10	Val Pro Ala	tcg gcg ccc Ser Ala Pro 1940	cac ccc cgc His Pro Arg 1945	ccg ctg cag Pro Leu Gln	gag gtg gag atg Glu Val Glu Met 1950	5856
15	gag acc tat Glu Thr Tyr 1955	ggg gcc ggc Gly Ala Gly	acc ccc ttg Thr Pro Leu 1960	Gly Ser Val	gcc tct gtg cac Ala Ser Val His 965	5904
20	tct ccg ccc Ser Pro Pro 1970	Ala Glu Ser	tgt gcc tcc Cys Ala Ser .975	ctc cag atc Leu Gln Ile 1980	cca ctg gct gtg Pro Leu Ala Val	5952
25	tcg tcc cca Ser Ser Pro 1985	gcc agg agc Ala Arg Ser 1990	ggc gag ccc Gly Glu Pro	ctc cac gcc Leu His Ala 1995	ctg tcc cct cgg Leu Ser Pro Arg 2009	6000
	ggc aca gcc Gly Thr Ala	cgc tcc ccc Arg Ser Pro 2005	Ser Leu Ser	cgg ctg ctc Arg Leu Leu 2010	tgc aga cag gag Cys Arg Gln Glu 2015	6048
30	Ala Val His	acc gat tcc Thr Asp Ser 2020	ttg aag gga Leu Lys Gly 2025	Arg Leu Thr	gcc cta ggg aca Ala Leu Gly Thr 2030	6096
35	ccc tgg atc Pro Trp Ile 2035	ctg cag agc Leu Gln Ser	ctg gtg aga Leu Val Arg 2040	aaa ccc cgg Lys Pro Arg		6132
40	<210> 10 <211> 6114 <212> DNA <213> Homo	sapiens				
45	<220> <221> CDS <222> (1)	(6114)				
50	<400> 10 atg acc gag Met Thr Glu 1	g ggc gca cgg n Gly Ala Arg 5	gcc gcc gac Ala Ala Asp	gag gtc cgg Glu Val Arg	gtg ccc ctg ggg Val Pro Leu Gly 15	48
55	cgc cgc ccc Arg Arg Pro	tgg ccc tgc Trp Pro Cys 20	ggc gtt ggt Gly Val Gly 25	Gly Gly Val	ccc gga gag ccc Pro Gly Glu Pro 30	96
60	cgg ggc gcc Arg Gly Ala 3	a Gly Thr Arg	ggc gga ggg Gly Gly Gly 40	g ggg ttc gag / Gly Phe Glu	ctc ggc gtg tca Leu Gly Val Ser 45	144
	-		acc asa ca	r tac aca asa	ctg ggt gcc gac	192

5	gag Glu 65	gag Glu	cag Gln	cgc Arg	gt: Val	ccg Pro 70	tac Tyr	ccg Pro	gcc Ala	ttg Leu	gcg Ala 75	Ala	acg Thr	gtc Val	ttc Phe	ttc Phe 80	240
	tgc Cys	ctc Leu	gg: Gly	cag Gln	acc Thr 85	acg Thr	cgg Arg	ccg Pro	cgc Arg	agc Ser 90	tgg Trp	tgc Cys	Ctc	cgg Arg	ctg Leu 95	gtc Val	288
10	tgc Cys	aac Asn	cca Pro	tgg Trp 100	ttc Phe	gag Glu	cac His	gtg Val	agc Ser 105	atg Met	ctg Leu	gta Val	atc Ile	atg Met 110	Leu	aac Asn	336
15	tgc Cys	gtg Val	acc Thr 115	ctg Leu	ggc Gly	atg Met	ttc Phe	cgg Arg 120	ccc Pro	tgt Cys	gag Glu	gac Asp	gtt Val 125	gag Glu	tgc Cys	ggc Gly	384
20	tcc Ser	gag Glu 130	cgc Arg	tgc Cys	aac Asn	atc Ile	ctg Leu 135	gag Glu	gcc Ala	ttt Phe	gac Asp	gcc Ala 140	ttc Phe	att Ile	ttc Phe	gcc Ala	432
25	ttt Phe 145	ttt Phe	gcg Ala	gtg Val	gag Glu	atg Met 150	gtc Val	atc Ile	aag Lys	atg Met	gtg Val 155	gcc Ala	ttg Leu	Gly	ctg Leu	ttc Phe 160	480
	ggg Gly	cag Gln	aag Lys	tgt Cys	tac Tyr 165	ctg Leu	ggt Gly	gac Asp	acg Thr	tgg Trp 170	aac Asn	agg Arg	ctg Leu	gat Asp	ttc Phe 175	ttc Phe	528
30	atc Ile	gtc Val	gtg Val	gcg Ala 180	ggc Gly	atg Met	atg Met	gag Glu	tac Tyr 185	tcg Ser	ttg Leu	gac Asp	gga Gly	cac His 190	aac Asn	gtg Val	576
35	agc Ser	ctc Leu	tcg Ser 195	gct Ala	atc Ile	agg Arg	acc Thr	gtg Val 200	cgg Arg	gtg Val	ctg Leu	cgg Arg	ccc Pro 205	ctc Leu	cgc Arg	gcc Ala	624
40	atc Ile	aac Asn 210	cgc Arg	gtg Val	cct Pro	agc Ser	atg Met 215	cgg Arg	atc Ile	ctg Leu	gtc Val	act Thr 220	ctg Leu	ctg Leu	ctg Leu	gat Asp	672
45	acg Thr 225	ctg Leu	ccc Pro	atg Met	ctc Leu	ggg Gly 230	aac Asn	gtc Val	ctt Leu	ctg Leu	ctg Leu 235	tgc Cys	ttc Phe	ttc Phe	gtc Val	ttc Phe 240	720
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	ccc Pro 305	Gly Ggc	cgc Arg	cgc Arg	gac Asp	gtg Val 310	cgc Arg	atg Met	ccc Pro	tgc Cys	acc Thr 315	ctg Leu	ggc Gly	tgg Trp	gag Glu	gcc Ala 320	960

5					cag Gln 325												1003
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10					gcc Ala												1104
15					gtg Val												1152
20					gcc Ala												1200
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					ttc Phe												1296
30					gca Ala									Leu			1344
35	ttc Phe	tcc Ser 450	gag Glu	cct Pro	ggc Gly	agc Ser	tgc Cys 455	tac Tyr	gaa Glu	gag Glu	ctg Leu	ctg Leu 460	aag Lys	tac Tyr	gtg Val	ggc Gly	1392
40					aag Lys												1440
45					tgg Trp 485												1488
	cag Gln	ggt Gly	ccc Pro	999 61y 500	cac His	cgc Arg	cag Gln	cgc Arg	cgg Arg 505	gca Ala	ggc Gly	agg Arg	cac His	aca Thr 510	gcc Ala	tcg Ser	1536
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55	cat His	ttc Phe 530	agc Ser	cat His	ggc Gly	agc Ser	ccc Pro 535	cgc Arg	agg Arg	ccc Pro	ggc Gly	ccc Pro 540	gag Glu	cca Pro	ggc Gly	gcc Ala	1632
60					ctg Leu												1680
					ccc Pro 565												1728

5	gcc Ala	gac Asp	tgc Cys	cac His 580	ata Ile	gag Glu	ggg	ccg Pro	cag Gln 585	gag Glu	agg Arg	gcc Ala	egg Arg	gtg Val 590	Gly	aca Thr	1776
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10	cac His	cat His 610	gaa Glu	cta Leu	ccc Pro	cac His	gat Asp 615	cct Pro	gcc Ala	ctc Leu	·agg Arg	ggt Gly 620	-ggg	cag Gln	cgg Arg	caa Gln	1872
15	agg Arg 625	cag Gln	cac His	cag Gln	ccc Pro	cgg Arg 630	acc Thr	caa Gln	G]A aaa	gaa Glu	gtg Val 635	ggc Gly	cgg Arg	tgg Trp	acc Thr	gcc Ala 640	1920
20	agg Arg	cac His	cgg Arg	G] À âââ	cac His 645	ggc Gly	ccg Pro	ttg Leu	agc Ser	ttg Leu 650	aac Asn	agc Ser	cct Pro	gat Asp	ccc Pro 655	tac Tyr	1968
25	gag Glu	aag Lys	atc Ile	ccg Pro 660	cat His	gtg Val	gcc Ala	Gly ggg	gag Glu 665	cat His	gga Gly	ctg Leu	ggc Gly	caa Gln 670	gcc Ala	cct Pro	2016
	ggc Gly	cat His	ctg Leu 675	tcg Ser	ggc Gly	ctc Leu	agt Ser	gtg Val 680	Pro	tgc Cys	ccc Pro	ctg Leu	ccc Pro 685	agc Ser	ccc Pro	cca Pro	2064
30	Ala	Gly 690	Thr	Leu	Thr	Cys	Glu 695	Leu	Lys	Ser	Cys	ccg Pro 700	Tyr	Cys	Thr	Arg	2112
35	Ala 705	Leu	Glu	Asp	Pro	Glu 710	Gly	Glu	Leu	Ser	Gly 715	tcg Ser	Glu	Ser	Gly	Asp 720	2160
40	tca Ser	gat Asp	ggc	cgt Arg	ggc Gly 725	gtc Val	tat Tyr	gaa Glu	ttc Phe	acg Thr 730	cag Gln	gac Asp	gtc Val	cgg Arg	cac His 735	ggt Gly	2208
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	cca Pro	Gly	cca Pro 755	ggc Gly	agc Ser	ccc Pro	cag Gln	cgg Arg 760	cgg Arg	gca Ala	cag Gln	cag Gln	agg Arg 765	gca Ala	gcc Ala	ccg Pro	2304
50	ggc Gly	gag Glu 770	cca Pro	ggc Gly	tgg Trp	atg Met	ggc Gly 775	cgc Arg	ctc Leu	tgg Trp	gtt Val	acc Thr 780	ttc Phe	agc Ser	ggc Gly	aag Lys	2352
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	ccc Pro	gag Glu	gag Glu	ctg Leu 820	act Thr	aat Asn	gct Ala	ctg Leu	gag Glu 325	atc Ile	agc Ser	aac Asn	atc Ile	gtg Val 830	ttc Phe	ạcc Thr	2496

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	ctg Leu	ggc Gly 850	tac Tyr	atc Ile	cgg Arg	aac Asn	ccg Pro 855	tac Tyr	aac Asn	atc Ile	ttc Phe	gac Asp 860	ggc Gly	ats	atc Ile	gtg Val	2592
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15				acc Thr													2688
20	ctg Leu	cca Pro	gcc Ala	ctg Leu 900	cgg Arg	cgc Arg	cag Gln	ctc Leu	gtg Val 905	gtg Val	ctg Leu	gtg Val	aag Lys	acc Thr 910	atg Met	gac Asp	2736
25				acc Thr													2784
	agc Ser	atc Ile 930	ctg Leu	ggc Gly	atg Met	cac His	ctt Leu 935	ttc Phe	ggc Gly	tgc Cys	aag Lys	ttc Phe 940	agc Ser	ctg Leu	aag Lys	aca Thr	2832
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35				gtc Val													2928
40	gtg Val	gtc Val	ctg Leu	tac Tyr 980	aac Asn	ggc Gly	atg Met	gcc Ala	tcc Ser 985	acc Thr	tcc Ser	tcc Ser	tgg Trp	gcc Ala 990	gcc Ala	ctc Leu	2976
45				gcc Ala			Thr					Val					3024
	Leu	gtg Val .010	gcc Ala	atc Ile	ctc Leu	Val	gag Glu 015	ggc Gly	ttc Phe	cag Gln	Ala	gag Glu .020	ggc Gly	gat Asp	gcc Ala	aac Asn	3072
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55				ctc Leu 1					Thr					Met			3168
60			Val	acc Thr .060				Thr					Ala				3216
		Pro		tca Ser			Gln					Cys					3264

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	gca gca Ala Ala 1105	a gca a Ala	gct Ala	Pro	ggg Gly 1110	acc Thr	cgc Arg	cac His	Trp	gag Glu 1115	Thr	aga Arg	agc Ser	Leu	cgg Arg 1120	3360
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20	gcg ccg Ala Pro	gcg Ala 1155	Cys	cag Gìn	tgt Cys	Gly	gaa Glu 1160	cgt Arg	gag Glu	tcc Ser	Leu	ctg Leu 1165	tct Ser	ggc Gly	gag Glu	3504
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5	aag Lys 134	Val	gtg Val	gcc Ala	ctg Leu	ggg Gly 1350	ctg Leu	ctg Leu	toc Ser	Gly	gag Glu 1355	cac His	gcc Ala	tac Tyr	Leu	cag Gln 1360	4080
	agc Ser	agc Ser	tgg Trp	Asn	ctg Leu 1365	ctg Leu	gat Asp	ggg ggg	Leu	ctg Leu 1370	gtg Val	ctg Leu	gtg Val	Ser	ctg Leu 1375	gtg Val	4128
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10	gtc Val	cca Pro 50	cac His	cca Pro	gac Asp	ctg Leu	gcg Ala 55	cct	att Ile	gcc Ala	ttc Phe	ttc Phe 60	tgc Cys	ctg Leu	cga Arg	cag Gln	192
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45	atc atc gac atc gtg gtg tcc ctg gcc tca gcc ggg gga gcc aag atc Ile Ile Asp Ile Val Val Ser Leu Ala Ser Ala Gly Gly Ala Lys Ile 1220 1225 1230	3696
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	tto tac cac tgt Phe Tyr His Cys 1300	ctg ggc gtg Leu Gly Val	gac acc ego Asp Thr Arg 1305	aac atc acc aac Asn Ile Thr Asn 1310	n Arg Ser
5	gac tgc atg gcc Asp Cys Met Ala 1315	Ala Asn Tyr	ege tgg gte Arg Trp Val 1320	cat cac asa tac His His Lys Tyr 1325	aac ttc 3984 Asn Phe
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15	gat ggt tgg gtg Asp Gly Trp Val 1345	aac atc atg Asn Ile Met 1350	Tyr Asn Gly	otg gat got gtt Leu Asp Ala Val 1355	gct gtg 4080 Ala Val 1360
20	gac cag cag cct Asp Gln Gln Pro	gtg acc aac Val Thr Asn 1365	cac aac ccc His Asn Pro 1370	tgg atg ctg ctg Trp Met Leu Leu	tac ttc 4128 Tyr Phe 1375
	atc tcc ttc ctg Ile Ser Phe Leu 1380	ctc atc gtc Leu Ile Val	agc ttc ttt Ser Phe Phe 1385	gtg ctc aac atg Val Leu Asn Met 1390	Phe Val
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40	cac His	ctg Leu	Asp	gac Asp 1700	agc Ser	aac Asn	aag Lys	gag Glu 1	gcg Ala .705	cag Gln	gag Glu	gac Asp	Ala	gag Glu 1710	atg Met	gat Asp	5136
	gcc Ala	Glu	ctc Leu 1715	gag Glu	ctg Leu	gag Glu	Met	gcc Ala .720	cat His	ggc Gly	ctg Leu	Gly	cct Pro 725	ggc Gly	ccg Pro	agg Arg	5184
45	Leu	cct Pro 1730	acc Thr	ggc Gly	tcc Ser	Pro	ggc Gly .735	gcc Ala	cct Pro	ggc Gly	Arg	999 Gly 1740	ccg Pro	gga Gly	ggg Gly	gcg Ala	5232
50		Gly			Asp			ggc Gly		Leu					Tyr		5280
55	cct Pro	gcc Ala	cag Gln	Glu	aac Asn .765	ctg Leu	tgg Trp	ctg Leu	Asp	agc Ser .770	gtc Val	tct Ser	tta Leu	Ile	atc Ile 1775	aag Lys	5328
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- <del>-</del>	atc Ile	Phe	cac His 1795	cac His	tac Tyr	tcc Ser	Ser	cct Pro .800	gcc Ala	ggc Gly	tgc Cys	Lys	aag Lys 1805	tgt Cys	cac His	cac His	5424

	gac Asp	aaq Lys 1810	Gln	gag Glu	aca Thr	ggt Gly	cct Pro 1815	Arg	cca Pro	tcc Ser	tg: Cys	tgg Trp 1820	Val	acg Thr	acc Thr	<u>:</u>	5469
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•		1 > C	_	(550	5)												
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20	gag Glu	ccg Pro	gga Gly	atc Ile 20	act Thr	gag Glu	cag Gln	ccg Pro	ggg Gly 25	ccc Pro	cgg Arg	agt Ser	ccc Pro	cct Pro 30	cca Pro	tcc Ser	96
25	cct Pro	cca Pro	ggc Gly 35	ctg Leu	gag Glu	gag Glu	cca Pro	ttg Leu 40	gaa Glu	gga Gly	acc Thr	aac Asn	cct Pro 45	gac Asp	gtc Val	cca Pro	144
30	cat His	cca Pro 50	gac Asp	ctg Leu	gct Ala	cct Pro	gtt Val 55	gct Ala	ttc Phe	ttc Phe	tgc Cys	ctg Leu 60	cgc Arg	cag Gln	acc Thr	acg Thr	192
35	agc Ser 65	cca Pro	cgg Arg	aac Asn	tgg Trp	tgc Cys 70	atc Ile	aag Lys	atg Met	gtt Val	tgt Cys 75	aac Asn	ccg Pro	tgg Trp	ttc Phe	gag Glu 80	240
	tgt Cys	gtg Val	agc Ser	atg Met	ctg Leu 85	gtt Val	att Ile	ctg Leu	ctg Leu	aac Asn 90	tgt Cys	gtg Val	acc Thr	ctg Leu	ggc Gly 95	atg Met	288
40	tac Tyr	cag Gln	cca Pro	tgt Cys 100	gat Asp	gac Asp	atg Met	gag Glu	tgc Cys 105	ctg Leu	tcg Ser	gac Asp	cgt Arg	tgc Cys 110	aag Lys	atc Ile	336
45	ctg Leu	cag Gln	gtc Val 115	ttc Phe	gat Asp	gac Asp	ttc Phe	atc Ile 120	ttc Phe	atc Ile	ttc Phe	ttt Phe	gcc Ala 125	atg Met	gag Glu	atg Met	384
50	gtg Val	ctt Leu 130	aag Lys	atg Met	gtg Val	gcc Ala	ctg Leu 135	ggc Gly	att Ile	ttt Phe	ggc Gly	aag Lys 140	aag Lys	tgc Cys	tac Tyr	ctc Leu	432
55	gga Gly 145	gac Asp	aca Thr	tgg Trp	aac Asn	cgc Arg 150	ctg Leu	gat Asp	ttc Phe	ttc Phe	att Ile 155	gtc Val	atg Met	gca Ala	GJ À G B B B B B B B B B B B B B B B B B B B	atg Met 160	480
	gtt Val	gag Glu	tac Tyr	tct Ser	ctg Leu 165	gac Asp	cta Leu	cag Gln	aac Asn	atc Ile 170	aac Asn	ctg Leu	tca Ser	gcc Ala	atc Ile 175	cgc Arg	528
60	act Thr	gtg Val	cgt Arg	gtc Val 180	ctg Leu	agg Arg	cct Pro	ctc Leu	aaa Lys 185	gcc Ala	atc Ile	aac Asn	cgt Arg	gta Val 190	ccc Pro	agc Ser	576
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5												atc Ile 220					672
10												cgc Arg					720
15												ccc Pro					768
13												tcc Ser					816
20												ctg Leu					864
25												gac Asp 300					912
30	cgc Arg 305	cag Gln	gac Asp	ctc Leu	aac Asn	gcc Ala 310	agc Ser	ggt Gly	ctg Leu	tgc Cys	gtc Val 315	aac Asn	tgg Trp	aac Asn	cgc Arg	tac Tyr 320	960
35												cac His					1008
												att Ile					1056
40	act Thr	ctg Leu	gaa Glu 355	ggc Gly	tgg Trp	gtg Val	gag Glu	lle 360	atg Met	tac Tyr	tat Tyr	gtg Val	atg Met 365	gac Asp	gca Ala	cat His	1104
45												atc Ile 380					1152
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.55												gag Glu					1248
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60	. tat Tyr	Ğlű										ctt Leu					1344
	cgc	cgt	gcc	cta	ggc	ctc	tac	cag	gcc	ctg	cag	aac	cgg	cgc	cag	gcc	1392

	Arg	Arg 450	Ala	Leu	Gly	Leu	Tyr 455	Gln	Ala	Leu	Gln	Asn 460	Arg	Arg	Gln	Ala	
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10	gag Glu	ccc	agc Ser	cac His	tgc Cys 485	aag Lys	ctg Leu	tgc Cys	cca Pro	cga Arg 490	cac His	agc Ser	Pro	ctg Leú	gac Asp 495	ccc Pro	1488
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10				tgc Cys													1584
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25	tct Ser 545	gca Ala	gag Glu	gcc Ala	gaa Glu	gcc Ala 550	aat Asn	ggg Gly	gat Asp	gga Gly	ctc Leu 555	cag Gln	agc Ser	agt Ser	gag Glu	gat Asp 560	1.680
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				gac Asp													1824
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55				aac Asn 660													2016
<i>J J</i>				gaa Glu													2064
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10	ctt Leu	GļĀ āāā	atg Met	cat His 740	atc Ile	ttt Phe	ggc Gly	tge Cys	aaa Lys 745	ttc Phe	agc Ser	ctc Leu	cgc Arg	acg Thr 750	gac Asp	acg Thr	2256
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	His	s Gl	u Se	r Le	u Let 965	u Sei	r Gl	/ Glu	ı Gly	y Gl: 97	y Gl	y Se:	r Cys	s Va	l Ar 97	g Ala 5	
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	gac Asp 102	reu	gga Gly	gag Glu	Leu	gtg Val 1030	ccc Pro	gtg Val	gtg Val	ggt Gly	gcc Ala 1035	His	tca Ser	cgç Arç	gco Ala	gct Ala 1040	3120
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<i>35</i>	• • •	cgc Arg 1090	aag Lys	atg Met	atț Ile	wab	gtg Val 1095	tac Tyr	aag Lys	ccg Pro	Asp	tgg Trp 1100	tgc Cys	gaa Glu	gtc Val	cgc Arg	3312
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	Ser	Val		Ser 1220	Ala	Gly	Gly		Lys 1225	Ile	Leu	Gly		Leu 1230	Arg	Val	
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10	Pro	ggg Gly L250	stg Leu	aag Lys	ctg Leu	gtg Val	gta Val 1255	gag Glu	acg Thr	Ctc Leu	Ile	tcc Ser 1260	tcc Ser	ctc Leu	aag Lys	ccc Pro	3792
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13	atc Ile	ctg Leu	GJ À ààà	Val	cag Gln 1285	ctt Leu	ttc Phe	aaa Lys	Gly	aag Lys 1290	ttc Phe	tac Tyr	cat His	Cys	ttg Leu 1295	gga Gly	3888
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	aac Asn	cac His	aac Asn	Pro	tgg Trp 1365	atg Met	cta Leu	ctg Leu	Tyr	ttc Phe 1370	att Ile	tcg Ser	ttc Phe	Leu	ctc Leu 1375	atc Ile	4128
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50	Glu	gag Glu 410	aaa Lys	cgg Arg	ctg Leu	cgg Arg	cgc Arg 415	ctg Leu	gaa Glu	aag Lys	Lys	cgc Arg 1420	cgt Arg	aag Lys	gct Ala	cag Gln	4272
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	tcc Ser	atg Met	tgc Cys	Thr	agc Ser 1445	cac His	tac Tyr	ctg Leu	Asp	atc Ile .450	ttc Phe	att Ile	acc Thr	Phe	atc Ile 1455	atc Ile	4368
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	tcc	cta	gag	aca	gcc	ctt	aag	tac	tgc	aac	tac	atg	ttc	acc	act	gta	4464

	Ser Leu 0 14	Glu Thr 175	Ala Leu	Lys Tyr 1480	Cys As:	. Tyr Met	: Phe Thr 1435	Thr Val	
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10	ttc ttc a Phe Phe L 1505	ag gac ys Asp	cga tgg Arg Trp 1510	aac cag Asn Gln	cig gac Leu Asp	ctg gcc Leu Ala 1515	att gtg Ile Val	ctg ctg Leu Leu 1520	4560
15	tee gte a Ser Val M	er erv .	atc aca Ile Thr : 525	ctg gag Leu Glu	gag ato Glu Ile 1530	Glu Ile	Asn Ala	gcc ctt Ala Leu 1535	4608
	ccc atc a Pro Ile A	ac ccc a sn Pro 1 1540	acc atc ( Thr Ile )	Ile Arg	atc atg Ile Met 1545	cgt gtt Arg Val	ctg cgt Leu Arg 1550	atc gcc Ile Ala	4656
20	cgg gtg t Arg Val L 15	eu Lys I	cta ttg a Leu Leu 1	aag atg Lys Met 1560	gcc aca Ala Thr	Gly Met	cgg gcc Arg Ala 1565	ctg ctg Leu Leu	4704
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10	gac acc Asp Thr	gag Glu	Ser	cac His 1765	ctg. Leu	tgc Cys	cgg Arg	His	tgc Cys 1770	tat Tyr	tct Ser	cca Pro	Ala	cag Gln 1775	gag Glu	5328
15	acc ctg Thr Leu	Trp	ctg Leu 1780	gac Asp	agc Ser	gtc Val	Ser	tta Leu 1785	atc Ile	atc Ile	aag Lys	Asp	tcc Ser 1790	ttg Leu	gag Glu	5376
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35	<400> 1 Ile Arg 1		Met	Arg 5	Val	Leu	Arg	Ile	Ala 10	Arg	Val	Leu	Lys	Leu 15	Leu	
	Lys Met	Ala														

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Intern Isl Application No PCT/US 98/23161

PCT/US 98/23161 A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C12N15/12 C07 C07K14/705 C07K16/28 C12N5/10 G01N33/68 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Category 1 Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. X WO 95 04144 A (NEUREX CORP) 1,2,7, 9 February 1995 10-18. 20-22 Υ see abstract; claims 1-10 3,19 X NOONEY JM (REPRINT) ET AL: "Identifying 1,2, neuronal non-L Ca2+ channels - more than 10-16, stamp collecting?" 20-22 TRENDS IN PHARMACOLOGICAL SCIENCES, 10-1997, 18, 363-371, XP002093637 see page 369, right-hand column - page 370, right-hand column Further documents are listed in the continuation of box C. Х Patent family members are listed in annex. Special categories of cited documents : "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the lart which is not considered to be of particular relevance invention earlier document but published on or after the international "X" document of particular relevance; the claimed invention filing date cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document which may throw doubts on pnority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu-"O" document referring to an oral disclosure, use, exhibition or other means ments, such combination being obvious to a person skilled in the art. document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 16 February 1999 09/03/1999 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl. Fax: (+31-70) 340-3016 Gurdjian, D

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